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[Continued on next page]

(54) Title: RECOMBINANT PARAINFLUENZA VIRUS EXPRESSION SYSTEMS AND VACCINES COMPRISING HETEROLOGOUS ANTIGENS DERIVED FROM METAPNEUMOVIRUS

Human 1 MSHKVVVIIISLLITPQHQLKESYLESSCSTTBYGLSVIRTOMYITIVVTLFVGQVENVILTC 60
M ++ + L + P ++B-Y EESCST-T QY SVLEKIGMTMIVP LE+G+V+S+TC 60
Turkey 1 MDOVRICLLFLPLISDVSSCIGETTVEEBCSTVTRGKYSVLAKGNTITMIVVSLIGQVENVITC 60
Human 61 ADOPSLIKITZELDLTKSALRERLTVSADQLARKEQIENPQQSRPFLVQIALOVATAAAVTA 120
DGPSPS IEL LTK+ALREL-TVSDAQKA+E + + PRPVPVQIALVATAAAVTA 120
Turkey 61 NDOPSLIKITZELDLTVLTKNALRELKVTSADQVAKCSRLSPLSPRRRPFVQIALOVATAAAVTA 120
Human 121 GVIAKAKTIRLESEBVTAIXKALAKTNEAVSTLGEVIEVLAATVRELEDV/SEN/TRAINIG 180
GVIA+AKTIRLE EV AKXAL- TNEAVSTLGEVIEVLAATV +LE+P-SK LT AII+N 180
Turkey 121 GVALVAKTIRLESEVKAKALAKTNEAVSTLGEVIEVLAATVNEDEKPISEKLTPAINQH 180
Human 181 KCDIADILOQAVSPSPVPPRPLNNVPROPSDAGITTPAISGQDQTDAAARAVSNSMPTSQQ 240
KC+IAD-KHA+SP Q MERPLAVVPROPS+AGIT A+SDLMKD EL RA++ MPT8+GQ 240
Turkey 181 KCNIAIDIQMAISPGQN+VPLAVVQFEDSGAGITSBASLDQDTEDEVLRAHQHNTSQQ 240
Human 241 IZKMLERTRANVRKGPOFLIGUVGSSVIYNVQPGVIDTPCWIVKQAPCSGKHZDYYA 300
I LML VRAMVERKING LIGVY +V+IVKOLPQVPI+TPCW V AP C +KHZYA 300
Turkey 241 ISBLMLNHRAMVRKGPOFLIGUVGSSVIYNVQPGVIDTPCWVRVVAAPLICRKHZDYYA 300
Human 301 CILREDQGYCNAQGSTVYYPNPKEDCTRGHVFCDTGAQINVARQSKNCMNP1STTYTP 360
C+LREDQGYCNAQGSTVYYPNPKEDCTRGHVFCDTGAQINVARQSKNCMNP1STTYTP 360
Turkey 301 CILREDQGYCNAQGSTVYYPNPKEDCTRGHVFCDTGAQINVARQSKNCMNP1STTYTP 360
Human 361 CKVSTGRHPISMVALSPLGALVACTKGVSCEISQSERVGI+KDLKQCGSYTISQDADFTI 420
CKVSTGRHPISMVALSPLGALVACTKGVSCEISQSERVGI+KDLKQCGSYTISQDADFTI 420
Turkey 361 CKVSTGRHPVPSNVALTPLOGLVCTYESVSC6ISGSIKVQVIIQKLGOKC7HPIPNADFTI 420
Human 421 INTVYQLSKVBEQGVHVKIGRPVGSSTFDVVKPFRDQFQFVALDQVYESIHSQALVDQSWRI 480
INTVYQLSKVBEQGVHVKIGRPVGSSTFDVVKPFRDQFQFVALDQVYESIHSQALVDQSWRI 480
Turkey 421 INTVYQLSKVBEQRTIGAPVPUZTSPVLFPEQDQFQFVALDQVYESIHSQALVDQSWRI 480
Human 481 LSSAREKNGTGFIVVIIILIAVQGSTNLVSVVII- IKTGCPGAPPLSGLGVMMGF 536
L + K G I I ++++LQ +L ++ ++KTK P P +O ++ ++
Turkey 481 LOADAKEXKGQIALIAVIVLVILOTIFPLLAIVTIVCSRVKTK-PKEDYPATGSSHAYV 537

(57) Abstract: The present invention relates to recombinant bovine parainfluenza virus (bPIV) cDNA or RNA which may be used to express heterologous gene products in appropriate host cell systems and/or to rescue negative strand RNA recombinant viruses that express, package, and/or present the heterologous gene product. In particular, the heterologous gene products include gene product of another species of PIV or from another negative strand RNA virus, including but not limited to, influenza virus, respiratory syncytial virus, human metapneumovirus and avian pneumovirus. The chimeric viruses and expression products may advantageously be used in vaccine formulations including vaccines against a broad range of pathogens and antigens.

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**RECOMBINANT PARAINFLUENZA VIRUS EXPRESSION
SYSTEMS AND VACCINES COMPRISING HETEROLOGOUS ANTIGENS
5 DERIVED FROM METAPNEUMOVIRUS**

This application claims priority to U.S. Provisional Patent Application No. 60/358,934, filed February 21, 2002, which is incorporated by reference herein in its entirety.

10 Copending and co-assigned U.S. Patent Application ___, filed on even date herewith, listing Ronaldus Fouchier, Bernadetta van den Hoogen, Albertus Osterhaus, Aurelia Haller, and Roderick Tang as Inventors, entitled "METAPNEUMOVIRUS STRAINS AND THEIR USE IN VACCINE FORMULATIONS AND AS VECTORS FOR EXPRESSION OF ANTIGENIC SEQUENCES", is incorporated herein by reference in its entirety.

15

1. INTRODUCTION

The present invention relates to recombinant parainfluenza virus (PIV) cDNA or RNA that may be used to express heterologous gene products in appropriate host cell systems and/or to rescue negative strand RNA recombinant viruses that express, package, and/or present the heterologous gene product. In particular, the present invention encompasses vaccine preparations comprising chimeric PIV expressing a heterologous gene product, wherein the heterologous gene product is preferably an antigenic peptide or polypeptide. In one embodiment, the PIV vector of the invention expresses one, two, or three heterologous gene products that may be encoded by the same or different viruses. In a preferred embodiment, the heterologous sequence encodes a heterologous gene product that is an antigenic polypeptide from another species of PIV or from another negative strand RNA virus, including but not limited to, influenza virus, respiratory syncytial virus (RSV), mammalian metapneumovirus, and avian pneumovirus. The vaccine preparations of the invention encompass multivalent vaccines, including bivalent and trivalent vaccine preparations. The multivalent vaccines of the invention may be administered in the form of one PIV vector expressing each heterologous antigenic sequence or two or more PIV vectors

each encoding different heterologous antigenic sequences. The vaccine preparations of the invention can be administered alone or in combination with other vaccines, prophylactic agents, or therapeutic agents.

5

2. BACKGROUND OF THE INVENTION

Parainfluenza viral infection results in serious respiratory tract disease in infants and children. (Tao *et al.*, 1999, Vaccine 17: 1100-08). Infectious parainfluenza viral infections account for approximately 20% of all hospitalizations of pediatric patients that suffer from 10 respiratory tract infections worldwide. *Id.* An effective antiviral therapy is not available to treat PIV related diseases, and a vaccine to prevent PIV infection has not yet been approved.

PIV is a member of the genus respirovirus (PIV1, PIV3) or rubulavirus (PIV2, PIV4) of the paramyxoviridae family. PIV is made up of two structural modules: (1) an internal ribonucleoprotein core, or nucleocapsid, containing the viral genome, and (2) an outer, 15 roughly spherical lipoprotein envelope. Its genome consists of a single strand of negative sense RNA, that is approximately 15,456 nucleotides in length and encodes at least eight polypeptides. These proteins include the nucleocapsid structural protein (NP, NC, or N depending on the genera), the phosphoprotein (P), the matrix protein (M), the fusion glycoprotein (F), the hemagglutinin-neuraminidase glycoprotein (HN), the large polymerase 20 protein (L), and the C and D proteins of unknown function. *Id.*

The parainfluenza nucleocapsid protein (NP, NC, or N) contains two domains within each protein unit. These domains include: an amino-terminal domain, that comprises nearly two-thirds of the molecule and interacts directly with the RNA, and a carboxyl-terminal domain, that lies on the surface of the assembled nucleocapsid. A hinge is thought to exist 25 at the junction of these two domains, thereby imparting some flexibility on this protein (see Fields *et al.* (ed.), 1991, FUNDAMENTAL VIROLOGY, 2nd ed, Raven Press, New York, incorporated by reference herein in its entirety). The matrix protein (M) is apparently involved in viral assembly, and it interacts with both the viral membrane and the nucleocapsid proteins. The phosphoprotein (P) is subject to phosphorylation and has been 30 implicated in transcription regulation, methylation, phosphorylation and polyadenylation. Produced initially as an inactive precursor, the fusion glycoprotein (F) is cleaved upon

translation to produce two disulfide linked polypeptides. The active F protein interacts with the viral membrane where it facilitates penetration of the parainfluenza virion into host cells by promoting the fusion of the viral envelope with the host cell plasma membrane. *Id.* The 5 glycoprotein, hemagglutinin-neuraminidase (HN) protrudes from the envelope and imparts hemagglutinin and neuraminidase activities on the virus. HN has a strongly hydrophobic amino terminus that functions to anchor the HN protein into the lipid bilayer. *Id.* Finally, the large polymerase protein (L) plays an important role in both transcription and replication.

Id.

10 Bovine parainfluenza virus was first isolated in 1959 from calves showing signs of shipping fever. It has since been isolated from normal cattle, aborted fetuses, and cattle exhibiting signs of respiratory disease (Breker-Klassen *et al.*, 1996, Can. J. Vet. Res. 60: 228-236. *See also* Shibuta, 1977, Microbiol. Immunol. 23 (7), 617-628). Human and bovine PIV3 share neutralizing epitopes but show distinct antigenic properties. Significant 15 differences exist between the human and bovine viral strains in the HN protein. In fact, a bovine strain induces some neutralizing antibodies to hPIV infection while a human strain seems to induce a wider spectrum of neutralizing antibodies against human PIV3 (Van Wyke Coelingh *et al.*, 1990, J. Virol. 64:3833-3843).

20 The replication of all negative-strand RNA viruses, including PIV, is complicated by the absence of the cellular machinery that is required to replicate RNA. Additionally, the negative-strand genome must be transcribed into a positive-strand (mRNA) copy before translation can occur. Consequently, the genomic RNA alone cannot synthesize the required RNA-dependent RNA polymerase upon entry into the cell. The L, P and N proteins must enter the host cell along with the genomic RNA.

25 It is hypothesized that most or all of the viral proteins that transcribe PIV mRNA also carry out the replication of the genome. The mechanism that regulates the alternative uses (*i.e.*, transcription or replication) of the same complement of proteins has not been clearly identified, but the process appears to involve the abundance of free forms of one or more of the nucleocapsid proteins. Directly following penetration of the virus, transcription is 30 initiated by the L protein using the negative-sense RNA in the nucleocapsid as a template.

Viral RNA synthesis is regulated such that it produces monocistronic mRNAs during transcription.

Following transcription, virus genome replication is the second essential event in
5 infection by negative-strand RNA viruses. As with other negative-strand RNA viruses, virus genome replication in PIV is mediated by virus-specified proteins. The first products of replicative RNA synthesis are complementary copies (*i.e.*, plus-polarity) of the PIV genomic RNA (cRNA). These plus-stranded copies (anti-genomes) differ from the plus-stranded mRNA transcripts in the structure of their termini. Unlike the mRNA transcripts, the anti-
10 genomic cRNAs are not capped or methylated at the 5' termini, and they are not truncated nor polyadenylated at the 3' termini. The cRNAs are coterminal with their negative strand templates and contain all the genetic information in the complementary form. The cRNAs serve as templates for the synthesis of PIV negative-strand viral genomes (vRNAs).

The bPIV negative strand genomes (vRNAs) and antigenomes (cRNAs) are
15 encapsidated by nucleocapsid proteins; the only unencapsidated RNA species are viral mRNAs. Replication and transcription of bPIV RNA occurs in the cytoplasm of the host cell. Assembly of the viral components appears to take place at the host cell plasma membrane where the mature virus is released by buddin-

20 **2.1. PARAMYXOVIRUS**

Classically, as devastating agents of disease, paramyxoviruses account for many animal and human deaths worldwide each year. The Paramyxoviridae form a family within the order of Mononegavirales (negative-sense single stranded RNA viruses), consisting of the sub-families Paramyxovirinae and Pneumovirinae. The latter sub-family is at present taxonomically divided in the genera Pneumovirus and Metapneumovirus (Pringle, 1999, Arch. Virol. 144/2, 2065-2070). Human respiratory syncytial virus (hRSV), a species of the Pneumovirus genus, is the single most important cause of lower respiratory tract infections during infancy and early childhood worldwide (Domachowske, & Rosenberg, 1999, Clin. Microbiol. Rev. 12(2): 298-309). Other members of the Pneumovirus genus include the bovine and ovine respiratory syncytial viruses and pneumonia virus of mice (PVM).

In the past decades several etiological agents of mammalian disease, in particular of respiratory tract illnesses (RTI), in particular of humans, have been identified (Evans, In: Viral Infections of Humans, Epidemiology and Control. 3th ed. (ed. Evans, A.S) 22-28
5 (Plenum Publishing Corporation, New York, 1989)). Classical etiological agents of RTI with mammals are respiratory syncytial viruses belonging to the genus Pneumovirus found with humans (hRSV) and ruminants such as cattle or sheep (bRSV and/or oRSV). In human RSV differences in reciprocal cross neutralization assays, reactivity of the G proteins in immunological assays and nucleotide sequences of the G gene are used to define two hRSV
10 antigenic subgroups. Within the subgroups the amino acid sequences show 94 % (subgroup A) or 98% (subgroup B) identity, while only 53% amino acid sequence identity is found between the subgroups. Additional variability is observed within subgroups based on monoclonal antibodies, RT-PCR assays and RNase protection assays. Viruses from both subgroups have a worldwide distribution and may occur during a single season. Infection
15 may occur in the presence of pre-existing immunity and the antigenic variation is not strictly required to allow re-infection. See, for example Sullender, 2000, Clinical Microbiology Reviews 13(1): 1-15; Collins et al. Fields Virology, ed. B.N. Knipe, Howley, P.M. 1996, Philadelphia: Lippencott-Raven. 1313-1351; Johnson et al., 1987, (Proc Natl Acad Sci USA, 84(16): 5625-9; Collins, in The Paramyxoviruses, D.W. Kingsbury, Editor. 1991, Plenum
20 Press: New York. p. 103-153.

Another classical Pneumovirus is the pneumonia virus of mice (PVM), in general only found with laboratory mice. However, a proportion of the illnesses observed among mammals can still not be attributed to known pathogens.

25

2.2. RSV INFECTIONS

Respiratory syncytial virus (RSV) is the leading cause of serious lower respiratory tract disease in infants and children (Feigen et al., eds., 1987, In: Textbook of Pediatric Infectious Diseases, WB Saunders, Philadelphia at pages 1653-1675; New Vaccine Development, Establishing Priorities, Vol. 1, 1985, National Academy Press, Washington DC at pages 397-409; and Ruuskanen *et al.*, 1993, Curr. Probl. Pediatr. 23:50-79). The yearly epidemic nature of RSV infection is evident worldwide, but the incidence and severity

of RSV disease in a given season vary by region (Hall, 1993, *Contemp. Pediatr.* 10:92-110). In temperate regions of the northern hemisphere, it usually begins in late fall and ends in late spring. Primary RSV infection occurs most often in children from 6 weeks to 2 years of age
5 and uncommonly in the first 4 weeks of life during nosocomial epidemics (Hall *et al.*, 1979, *New Engl. J. Med.* 300:393-396). Children at increased risk for RSV infection include, but are not limited to, preterm infants (Hall *et al.*, 1979, *New Engl. J. Med.* 300:393-396) and children with bronchopulmonary dysplasia (Groothuis *et al.*, 1988, *Pediatrics* 82:199-203), congenital heart disease (MacDonald *et al.*, *New Engl. J. Med.* 307:397-400), congenital or
10 acquired immunodeficiency (Ogra *et al.*, 1988, *Pediatr. Infect. Dis. J.* 7:246-249; and Pohl *et al.*, 1992, *J. Infect. Dis.* 165:166-169), and cystic fibrosis (Abman *et al.*, 1988, *J. Pediatr.* 113:826-830). The fatality rate in infants with heart or lung disease who are hospitalized with RSV infection is 3%-4% (Navas *et al.*, 1992, *J. Pediatr.* 121:348-354).

RSV infects adults as well as infants and children. In healthy adults, RSV causes
15 predominantly upper respiratory tract disease. It has recently become evident that some adults, especially the elderly, have symptomatic RSV infections more frequently than had been previously reported (Evans, A.S., eds., 1989, *Viral Infections of Humans. Epidemiology and Control*, 3rd ed., Plenum Medical Book, New York at pages 525-544).

Several epidemics also have been reported among nursing home patients and
20 institutionalized young adults (Falsey, A.R., 1991, *Infect. Control Hosp. Epidemiol.* 12:602-608; and Garvie *et al.*, 1980, *Br. Med. J.* 281:1253-1254). Finally, RSV may cause serious disease in immunosuppressed persons, particularly bone marrow transplant patients (Hertz *et al.*, 1989, *Medicine* 68:269-281).

Treatment options for established RSV disease are limited. Severe RSV disease of
25 the lower respiratory tract often requires considerable supportive care, including administration of humidified oxygen and respiratory assistance (Fields *et al.*, eds., 1990, *Fields Virology*, 2nd ed., Vol. 1, Raven Press, New York at pages 1045-1072).

While a vaccine might prevent RSV infection, and/or RSV-related disease, no
30 vaccine is yet licensed for this indication. A major obstacle to vaccine development is safety. A formalin-inactivated vaccine, though immunogenic, unexpectedly caused a higher and more severe incidence of lower respiratory tract disease due to RSV in immunized

infants than in infants immunized with a similarly prepared trivalent parainfluenza vaccine (Kim et al., 1969, Am. J. Epidemiol. 89:422-434; and Kapikian *et al.*, 1969, Am. J. Epidemiol. 89:405-421). Several candidate RSV vaccines have been abandoned and others
5 are under development (Murphy et al., 1994, Virus Res. 32:13-36), but even if safety issues are resolved, vaccine efficacy must also be improved. A number of problems remain to be solved. Immunization would be required in the immediate neonatal period since the peak incidence of lower respiratory tract disease occurs at 2-5 months of age. The immaturity of the neonatal immune response together with high titers of maternally acquired RSV antibody
10 may be expected to reduce vaccine immunogenicity in the neonatal period (Murphy et al., 1988, J. Virol. 62:3907-3910; and Murphy et al., 1991, Vaccine 9:185-189). Finally, primary RSV infection and disease do not protect well against subsequent RSV disease (Henderson et al., 1979, New Engl. J. Med. 300:530-534).

15 Currently, the only approved approach to prophylaxis of RSV disease is passive immunization. Initial evidence suggesting a protective role for IgG was obtained from observations involving maternal antibody in ferrets (Prince, G.A., Ph.D. diss., University of California, Los Angeles, 1975) and humans (Lambrecht *et al.*, 1976, J. Infect. Dis. 134:211-217; and Glezen et al., 1981, J. Pediatr. 98:708-715). Hemming et al. (Morell *et al.*, eds., 1986, Clinical Use of Intravenous Immunoglobulins, Academic Press, London at
20 pages 285-294) recognized the possible utility of RSV antibody in treatment or prevention of RSV infection during studies involving the pharmacokinetics of an intravenous immune globulin (IVIG) in newborns suspected of having neonatal sepsis. In this study, it was noted that one infant, whose respiratory secretions yielded RSV, recovered rapidly after IVIG infusion. Subsequent analysis of the IVIG lot revealed an unusually high titer of RSV
25 neutralizing antibody. This same group of investigators then examined the ability of hyperimmune serum or immune globulin, enriched for RSV neutralizing antibody, to protect cotton rats and primates against RSV infection (Prince et al., 1985, Virus Res. 3:193-206; Prince et al., 1990, J. Virol. 64:3091-3092; Hemming et al., 1985, J. Infect. Dis. 152:1083-1087; Prince et al., 1983, Infect. Immun. 42:81-87; and Prince et al., 1985, J.
30 Virol. 55:517-520). Results of these studies indicate that IVIG may be used to prevent RSV infection, in addition to treating or preventing RSV-related disorders.

Recent clinical studies have demonstrated the ability of this passively administered RSV hyperimmune globulin (RSV IVIG) to protect at-risk children from severe lower respiratory infection by RSV (Groothius et al., 1993, New Engl. J. Med. 329:1524-1530; and 5 The PREVENT Study Group, 1997, Pediatrics 99:93-99). While this is a major advance in preventing RSV infection, this treatment poses certain limitations in its widespread use. First, RSV IVIG must be infused intravenously over several hours to achieve an effective dose. Second, the concentrations of active material in hyperimmune globulins are insufficient to treat adults at risk or most children with compromised cardiopulmonary function. 10 Third, intravenous infusion necessitates monthly hospital visits during the RSV season. Finally, it may prove difficult to select sufficient donors to produce a hyperimmune globulin for RSV to meet the demand for this product. Currently, only approximately 8% of normal donors have RSV neutralizing antibody titers high enough to qualify for the production of 15 hyperimmune globulin.

15 One way to improve the specific activity of the immunoglobulin would be to develop one or more highly potent RSV neutralizing monoclonal antibodies (MAbs). Such MAbs should be human or humanized in order to retain favorable pharmacokinetics and to avoid generating a human anti-mouse antibody response, as repeat dosing would be required throughout the RSV season. Two glycoproteins, F and G, on the surface of RSV have been 20 shown to be targets of neutralizing antibodies (Fields et al., 1990, *supra*; and Murphy et al., 1994, *supra*).

A humanized antibody directed to an epitope in the A antigenic site of the F protein of RSV, SYNAGIS®, is approved for intramuscular administration to pediatric patients for prevention of serious lower respiratory tract disease caused by RSV at recommended 25 monthly doses of 15 mg/kg of body weight throughout the RSV season (November through April in the northern hemisphere). SYNAGIS® is a composite of human (95%) and murine (5%) antibody sequences. See, Johnson et al., 1997, *J. Infect. Diseases* 176:1215-1224 and U.S. Patent No. 5,824,307, the entire contents of which are incorporated herein by reference. The human heavy chain sequence was derived from the constant domains of human IgG1 30 and the variable framework regions of the VH genes of Cor (Press et al., 1970, *Biochem. J.* 117:641-660) and Cess (Takashi et al., 1984, *Proc. Natl. Acad. Sci. USA* 81:194-198). The

human light chain sequence was derived from the constant domain of C and the variable framework regions of the VL gene K104 with J -4 (Bentley et al., 1980, Nature 288:5194-5198). The murine sequences derived from a murine monoclonal antibody, Mab 5 1129 (Beeler et al., 1989, J. Virology 63:2941-2950), in a process which involved the grafting of the murine complementarity determining regions into the human antibody frameworks.

2.3. AVIAN PNEUMOVIRUSES

10 Respiratory disease caused by an avian pneumovirus (APV) was first described in South Africa in the late 1970s (Buys et al., 1980, Turkey 28:36-46) where it had a devastating effect on the turkey industry. The disease in turkeys was characterized by sinusitis and rhinitis and was called turkey rhinotracheitis (TRT). The European isolates of APV have also been strongly implicated as factors in swollen head syndrome (SHS) in 15 chickens (O'Brien, 1985, Vet. Rec. 117:619-620). Originally, the disease appeared in broiler chicken flocks infected with Newcastle disease virus (NDV) and was assumed to be a secondary problem associated with Newcastle disease (ND). Antibody against European APV was detected in affected chickens after the onset of SHS (Cook et al., 1988, Avian Pathol. 17:403-410), thus implicating APV as the cause.

20 Avian pneumovirus (APV) also known as turkey rhinotracheitis virus (TRTV), the aetiological agent of avian rhinotracheitis, an upper respiratory tract infection of turkeys (Giraud et al., 1986, Vet. Res. 119:606-607), is the sole member of the recently assigned Metapneumovirus genus, which, as said was until now not associated with infections, or what is more, with disease of mammals. Serological subgroups of APV can be 25 differentiated on the basis of nucleotide or amino acid sequences of the G glycoprotein and neutralization tests using monoclonal antibodies that also recognize the G glycoprotein. However, other differences in the nucleotide and amino acid sequences can be used to distinguish serological subgroups of APV. Within subgroups A, B and D, the G protein shows 98.5 to 99.7% aa sequence identity within subgroups while between the subgroups 30 only 31.2- 38% aa identity is observed. See for example Collins et al., 1993, Avian Pathology, 22: p. 469-479; Cook et al., 1993, Avian Pathology, 22: 257-273;

Bayon-Auboyer et al., J Gen Virol, 81(Pt 11): 2723-33; Seal, 1998, Virus Res, 58(1-2): 45-52; Bayon-Auboyer et al., 1999, Arch Virol, 144(6): 91-109; Juhasz, et al., 1994, J Gen Virol, 75(Pt 11): 2873-80.

5 A further serotype of APV is provided in WO00/20600, incorporated by reference herein, which describes the Colorado isolate of APV and compared it to known APV or TRT strains with in vitro serum neutralization tests. First, the Colorado isolate was tested against monospecific polyclonal antisera to recognized TRT isolates. The Colorado isolate was not neutralized by monospecific antisera to any of the TRT strains. It was, however, neutralized
10 by a hyperimmune antiserum raised against a subgroup A strain. This antiserum neutralized the homologous virus to a titre of 1:400 and the Colorado isolate to a titer of 1: 80. Using the above method, the Colorado isolate was then tested against TRT monoclonal antibodies. In each case, the reciprocal neutralization titer was <10. Monospecific antiserum raised to the Colorado isolate was also tested against TRT strains of both subgroups. None of the
15 TRT strains tested were neutralized by the antiserum to the Colorado isolate.

The Colorado strain of APV does not protect SPF chicks against challenge with either a subgroup A or a subgroup B strain of TRT virus. These results suggest that the Colorado isolate may be the first example of a further serotype of avian pneumovirus (See, Bayon-Auboyer et al., 2000, J. Gen. Vir. 81:2723-2733).

20 The avian pneumovirus is a single stranded, non-segmented RNA virus that belongs to the sub-family Pneumovirinae of the family Paramyxoviridae, genus metapneumovirus (Cavanagh and Barrett, 1988, Virus Res. 11:241-256; Ling et al., 1992, J. Gen. Virol. 73:1709-1715; Yu et al., 1992, J. Gen. Virol. 73:1355-1363). The Paramyxoviridae family is divided into two sub-families: the Paramyxovirinae and Pneumovirinae. The subfamily
25 Paramyxovirinae includes, but is not limited to, the genera: Paramyxovirus, Rubulavirus, and Morbillivirus. Recently, the sub-family Pneumovirinae was divided into two genera based on gene order, and sequence homology, i.e. pneumovirus and metapneumovirus (Naylor et al., 1998, J. Gen. Virol., 79:1393-1398; Pringle, 1998, Arch. Virol. 143:1449-1159). The pneumovirus genus includes, but is not limited to, human respiratory syncytial virus (hRSV), bovine respiratory syncytial virus (bRSV), ovine respiratory syncytial virus, and mouse pneumovirus. The metapneumovirus genus includes, but is not
30

limited to, European avian pneumovirus (subgroups A and B), which is distinguished from hRSV, the type species for the genus pneumovirus (Naylor et al., 1998, J. Gen. Virol., 79:1393-1398; Pringle, 1998, Arch. Virol. 143:1449-1159). The US isolate of APV
5 represents a third subgroup (subgroup C) within metapneumovirus genus because it has been found to be antigenically and genetically different from European isolates (Seal, 1998, Virus Res. 58:45-52; Senne et al., 1998, In: Proc. 47th WPDC, California, pp. 67-68).

Electron microscopic examination of negatively stained APV reveals pleomorphic, sometimes spherical, virions ranging from 80 to 200 nm in diameter with long filaments
10 ranging from 1000 to 2000 nm in length (Collins and Gough, 1988, J. Gen. Virol. 69:909-916). The envelope is made of a membrane studded with spikes 13 to 15 nm in length. The nucleocapsid is helical, 14 nm in diameter and has 7 nm pitch. The nucleocapsid diameter is smaller than that of the genera Paramyxovirus and Morbillivirus, which usually have diameters of about 18 nm.
15

Avian pneumovirus infection is an emerging disease in the USA despite its presence elsewhere in the world in poultry for many years. In May 1996, a highly contagious respiratory disease of turkeys appeared in Colorado, and an APV was subsequently isolated at the National Veterinary Services Laboratory (NVSL) in Ames, Iowa (Senne et al., 1997, Proc. 134th Ann. Mtg., AVMA, pp. 190). Prior to this time, the United States and Canada
20 were considered free of avian pneumovirus (Pearson et al., 1993, In: Newly Emerging and Re-emerging Avian Diseases: Applied Research and Practical Applications for Diagnosis and Control, pp. 78-83; Hecker and Myers, 1993, Vet. Rec. 132:172). Early in 1997, the presence of APV was detected serologically in turkeys in Minnesota. By the time the first confirmed diagnosis was made, APV infections had already spread to many farms. The
25 disease is associated with clinical signs in the upper respiratory tract: foamy eyes, nasal discharge and swelling of the sinuses. It is exacerbated by secondary infections. Morbidity in infected birds can be as high as 100%. The mortality can range from 1 to 90% and is highest in six to twelve week old pouls.

Avian pneumovirus is transmitted by contact. Nasal discharge, movement of
30 affected birds, contaminated water, contaminated equipment; contaminated feed trucks and load-out activities can contribute to the transmission of the virus. Recovered turkeys are

thought to be carriers. Because the virus is shown to infect the epithelium of the oviduct of laying turkeys and because APV has been detected in young pouls, egg transmission is considered a possibility.

5

A significant portion of human respiratory disease is caused by members of the viral sub-families Paramyxovirinae and Pneumovirinae, there still remains a need for an effective vaccine to confer protection against a variety of viruses that result in respiratory tract infection.

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Citation or discussion of a reference herein shall not be construed as an admission that such is prior art to the present invention.

3. SUMMARY OF THE INVENTION

The present invention relates to recombinant parainfluenza virus cDNA and RNA that may be engineered to express heterologous or non-native gene products, in particular, to express antigenic polypeptides and peptides. In one embodiment, the present invention relates to recombinant bovine or human parainfluenza viruses which are engineered to express heterologous antigens or immunogenic and/or antigenic fragments of heterologous antigens. In another embodiment of the invention, the recombinant bovine or human parainfluenza viruses are engineered to express sequences that are non-native to the PIV genome, including mutated PIV nucleotide sequences. In particular, the invention relates to recombinant Kansas-strain bovine parainfluenza type 3 virus as well as cDNA and RNA molecules coding for the same. The present invention also relates to recombinant PIV that contain modifications that result in chimeric viruses with phenotypes more suitable for use in vaccine formulations.

25

The present invention provides for the first time a chimeric PIV formulated as a vaccine that is able to confer protection against various viral infections, in particular, viruses that result in respiratory tract infections. In a specific embodiment, the present invention provides a vaccine that is able to confer protection against parainfluenza, influenza, or respiratory syncytial viral infection. The present invention provides for the first time a vaccine that is able to confer protection against metapneumovirus infection in a mammalian host.

In accordance with the present invention, a recombinant virus is one derived from a bovine parainfluenza virus or a human parainfluenza virus that is encoded by endogenous or native genomic sequences or non-native genomic sequences. In accordance with the 5 invention, a non-native sequence is one that is different from the native or endogenous genomic sequence due to one or more mutations, including, but not limited to, point mutations, rearrangements, insertions, deletions, etc. to the genomic sequence that may or may not result in a phenotypic change.

In accordance with the present invention, a chimeric virus of the invention is a 10 recombinant bPIV or hPIV which further comprises one or more heterologous nucleotide sequences. In accordance with the invention, a chimeric virus may be encoded by a nucleotide sequence in which heterologous nucleotide sequences have been added to the genome or in which nucleotide sequences have been replaced with heterologous nucleotide sequences.

The present invention also relates to engineered recombinant parainfluenza viruses 15 and viral vectors that encode combinations of heterologous sequences which encode gene products, including but not limited to, genes from different strains of PIV, influenza virus, respiratory syncytial virus, mammalian metapneumovirus (e.g., human metapneumovirus), avian pneumovirus, measles, mumps, other viruses, pathogens, cellular genes, tumor 20 antigens, or combinations thereof. Furthermore, the invention relates to engineered recombinant parainfluenza viruses that contain a nucleotide sequence derived from a metapneumovirus in combination with a nucleotide sequence derived from a respiratory syncytial virus, and further in combination with a nucleotide sequence derived from a human 25 parainfluenza virus. The invention also encompasses recombinant parainfluenza vectors and viruses that are engineered to encode genes from different species and strains of the parainfluenza virus, including the F and HN genes of human PIV3.

In one embodiment, the PIV vector of the invention is engineered to express one or 30 more heterologous sequences, wherein the heterologous sequences encode gene products that are preferably antigenic gene products. In a preferred embodiment, the PIV vector of the invention expresses one, two or three heterologous sequences that encode antigenic polypeptides and peptides. In some embodiments, the heterologous sequences are derived

from the same virus or from different viruses. In a preferred embodiment, the heterologous sequences encode heterologous gene products that are antigenic polypeptides from another species of PIV, such as a human PIV, a mutant strain of PIV, or from another negative strand 5 RNA virus, including but not limited to, influenza virus, respiratory syncytial virus (RSV), mammalian metapneumovirus (*e.g.*, human metapneumovirus (hMPV)), and avian pneumovirus. In one embodiment, the heterologous sequence encodes an immunogenic and/or antigenic fragment of a heterologous gene product.

In a preferred embodiment, the recombinant PIV is a bovine PIV type 3, or an 10 attenuated human PIV type 3. In one embodiment, the sequences encoding fusion (F) protein, hemagglutinin (HN) glycoprotein, or other non-essential genes of the PIV genome are deleted and are substituted by heterologous antigenic sequences. In yet another embodiment, the PIV genome contains mutations or modifications, in addition to the 15 heterologous nucleotide sequences, that result in a chimeric virus having a phenotype that is more suitable for use in vaccine formulations, *e.g.*, an attenuated phenotype or a phenotype with enhanced antigenicity.

In a specific embodiment, the heterologous nucleotide sequence to be inserted into the PIV genome is derived from the nucleotide sequences encoding a F protein, a G protein or an HN protein. In certain embodiments, the nucleotide sequence to be inserted encodes a 20 chimeric F protein, a chimeric G protein or a chimeric HN protein. In a specific embodiment, the F protein comprises an ectodomain of a F protein of a metapneumovirus, a transmembrane domain of a F protein of a parainfluenza virus, and a luminal domain of a F protein of a parainfluenza virus. In certain embodiments, the nucleotide sequence to be inserted encodes a F protein, wherein the transmembrane domain of the F protein is deleted 25 so that a soluble F protein is expressed.

In another specific embodiment, the invention provides a chimeric virus comprising a PIV genome comprising a heterologous nucleotide sequence derived from a metapneumovirus. In a specific embodiment, the PIV virus is a Kansas-strain bovine parainfluenza type 3 virus. In other embodiments, the PIV virus is a human parainfluenza 30 virus with an attenuated phenotype. In yet other embodiments, the invention provides a chimeric bovine parainfluenza virus type 3/human parainfluenza virus engineered to contain

5 human parainfluenza F and HN genes in a bovine parainfluenza backbone. The chimeric virus may further comprise a heterologous nucleotide sequence derived from a metapneumovirus, and/or further comprise a heterologous nucleotide sequence derived from
a respiratory syncytial virus.

10 In certain embodiments, the virus of the invention comprises heterologous nucleotide sequences derived from at least two different genes of a metapneumovirus. In a specific embodiment, the heterologous sequence is derived from a metapneumovirus, e.g., avian pneumovirus and human metapneumovirus. More specifically, the heterologous sequence is derived from an avian pneumovirus, including avian pneumovirus type A, B, C or D, preferably C.

15 The present invention also provides vaccine preparations and immunogenic compositions comprising chimeric PIV expressing one or more heterologous antigenic sequences. In a specific embodiment, the present invention provides multivalent vaccines, including bivalent and trivalent vaccines. The multivalent vaccines of the invention may be administered in the form of one PIV vector expressing each heterologous antigenic sequence or two or more PIV vectors each encoding different heterologous antigenic sequences. In one embodiment, the vaccine preparation of the invention comprises chimeric PIV expressing one, two or three heterologous polypeptides, wherein the heterologous polypeptides can be encoded by sequences derived from one strain of the same virus, different strains of the same virus, or different viruses. Preferably, the heterologous antigenic sequences are derived from a negative strand RNA virus, including but not limited to, influenza virus, parainfluenza virus, respiratory syncytial virus (RSV), mammalian metapneumovirus (e.g., human metapneumovirus (hMPV)), and avian pneumovirus (APV).
20 The heterologous antigenic sequences include, but are not limited to, sequences that encode human parainfluenza virus F or HN protein, F protein of RSV, HA protein of influenza virus type A, B, and C, and F protein of human MPV and avian pneumovirus. More preferably, the vaccine preparation of the invention comprises attenuated chimeric viruses that are viable and infectious. In a preferred embodiment, the recombinant PIV is a bovine PIV type
25 3, or an attenuated strain of human PIV.

In one embodiment, the vaccine preparation comprises the chimeric virus of the present invention, wherein the F, HN, or some other nonessential genes of the PIV genome have been substituted or deleted. In a preferred embodiment, the vaccine preparation of the present invention is prepared by engineering a strain of PIV with an attenuated phenotype in an intended host. In another preferred embodiment, the vaccine preparation of the present invention is prepared by engineering an attenuated strain of PIV.

In another embodiment, the heterologous nucleotide sequence is added to the complete PIV genome. In certain embodiments, the PIV genome is engineered so that the heterologous sequences are inserted at position one, two, three, four, five or six, so that the heterologous sequences are expressed as the first, second, third, fourth, fifth, or sixth gene of the viral genome. In specific embodiments, the heterologous sequence is inserted at position one, two, or three of the viral genome. In certain embodiments, the intergenic region between the end of the coding sequence of an inserted heterologous gene and the start of the coding sequence of the downstream gene is altered to a desirable length, resulting in enhanced expression of the heterologous sequence or enhanced growth of the chimeric virus. Alternatively, the intergenic region is altered to a desirable length, with a potential to alter the expression of the heterologous sequence or growth of the recombinant or chimeric virus, e.g., attenuated phenotype. In some embodiments, both the position of the insertion and the length of the intergenic region flanking a heterologous nucleotide sequence are engineered to select a recombinant or chimeric virus with desirable levels of expression of the heterologous sequence and desirable viral growth characteristics.

In certain embodiments, the invention provides a vaccine formulation comprising the recombinant or chimeric virus of the invention and a pharmaceutically acceptable excipient. In specific embodiments, the vaccine formulation of the invention is used to modulate the immune response of a subject, such as a human, a primate, a horse, a cow, a sheep, a pig, a goat, a dog, a cat, a rodent or a subject of avian species. In a more specific embodiment, the vaccine is used to modulate the immune response of a human infant or a child. In another embodiment, the present invention relates to vaccine formulations for veterinary uses. The vaccine preparation of the invention can be administered alone or in combination with other vaccines or other prophylactic or therapeutic agents.

3.1. CONVENTIONS AND ABBREVIATIONS

	cDNA	complementary DNA
5	CPE	cytopathic effects
	L	large protein
	M	matrix protein (lines inside of envelope)
	F	fusion glycoprotein
10	HN	hemagglutinin-neuraminidase glycoprotein
	N, NP or NC	nucleoprotein (associated with RNA and required for polymerase activity)
	P	phosphoprotein
	MOI	multiplicity of infection
15	NA	neuraminidase (envelope glycoprotein)
	PIV	parainfluenza virus
	bPIV	bovine parainfluenza virus
	bPIV3	bovine parainfluenza virus type 3
	hPIV	human parainfluenza virus
20	hPIV3	human parainfluenza virus type 3
	bPIV/hPIV or b/h PIV	recombinant bPIV with hPIV sequences
	b/h PIV3 or bPIV3/hPIV3	recombinant bPIV type 3 with hPIV type 3 sequences
25	nt	nucleotide
	RNP	ribonucleoprotein
	rRNP	recombinant RNP
	vRNA	genomic virus RNA
	cRNA	antigenomic virus RNA
30	hMPV	human metapneumovirus

	APV	avian pneumovirus
	position	when position is used regarding engineering any virus, it refers to the position of the gene of the viral genome to be transcribed. For example, if a gene is located at position one, it is the first gene of the viral genome to be transcribe; if a gene is located at position two, it is the second gene of the viral genome to be transcribed.
5		
10	position 1 of bPIV3, b/h PIV3 and derivatives thereof	nucleotide position 104 of the genome, or alternatively, the position of the first gene of the viral genome to be transcribed
15	position 2 of bPIV3, b/h PIV3 and derivatives thereof	nucleotide position 1774 of the genome, or alternatively the position between the first and the second open reading frame of the native parainfluenza virus, or alternatively, the position of the second gene of the viral genome to be transcribed
20	position 3 of bPIV3, b/h PIV3 and derivatives thereof	nucleotide position 3724 of the genome, or alternatively the position between the second and the third open reading frame of the native parainfluenza virus, or alternatively, the position of the third gene of the viral genome to be transcribed.
25	position 4 of bPIV3, b/h PIV3 and derivatives thereof	nucleotide position 5042 of the genome, or alternatively the position between the third and the fourth open reading frame of the native parainfluenza virus, or alternatively, the position of the fourth gene of the viral genome to be transcribed.
30	position 5 of bPIV3, b/h PIV3 and derivatives thereof	nucleotide position 6790 of the genome, or alternatively the position between the fourth and the fifth open reading frame of the native parainfluenza virus, or alternatively, the position of the fifth gene of the viral genome to be transcribed.
	position 6 of bPIV3, b/h PIV3 and derivatives thereof	nucleotide position 8631 of the genome, or alternatively the position between the fifth and the sixth open reading frame of the native parainfluenza virus, or alternatively, the position of the sixth gene of the viral genome to be transcribed.

4. DESCRIPTION OF FIGURES

Figure 1. Pairwise alignments of the amino acid sequence of the F protein of the human metapneumovirus with different F proteins from different avian pneumoviruses.

5 Identical amino acids between the two sequences are indicated by the one-letter-symbol for the amino acid. Conserved amino acid exchanges between the two amino acid sequences are indicated by a "+" sign, and a space indicates a non-conserved amino acid exchange. A) Alignment of the human metapneumoviral F protein with the F protein of an avian pneumovirus isolated from Mallard Duck (85.6% identity in the ectodomain). B) Alignment 10 of the human metapneumoviral F protein with the F protein of an avian pneumovirus isolated from Turkey (subgroup B; 75% identity in the ectodomain).

Figure 2. PCR fragments from nt 5255 to nt 6255 derived from three different isolates of the b/h PIV3 chimeric virus were amplified. The resulting 1 kb DNA fragments 15 were digested with enzymes specific for the F gene of human PIV3. These enzymes do not cut in the corresponding fragment of bovine PIV3. The 1% agarose gel shows the undigested fragment (lanes 2,5, and 6) and the SacI or BgIII digested fragments (lanes 4, 6 and lanes 9, 10, and 11, respectively). The sample in lane 10 is undigested, however, upon a repeat of digestion with BgIII, this sample was cut (data not shown). Lanes 1 and 8 show a 20 DNA size marker.

Figure 3. PCR fragments from nt 9075 to nt 10469 derived from three different isolates of the b/h PIV3 chimeric virus were amplified. The resulting 1.4kb DNA fragments were digested with enzymes specific for the L gene of bovine PIV3. These enzymes do not 25 cut in the corresponding fragment of human PIV3. The 1% agarose gel shows the undigested 1.4 kb fragment (lanes 2, 5, and 8). The smaller DNA fragments produced by digestion with BamH1 and PvuII are shown in lanes 3, 4, 6, 7, 9, and 10). Lane 1 shows a DNA size marker.

30 Figure 4. Six constructs, including the bPIV3/hPIV3 vector and b/h PIV3 vectored RSV F or G cDNA, are demonstrated. The bovine PIV3 F gene and HN gene are deleted

and replaced with human PIV3 F and HN gene respectively. The RSV F or G genes are cloned into either position 1 or position 2. All RSV genes are linked to the bPIV3 N-P intergenic region with the exception of RSV F1* (N-N), which is followed by the shorter
5 bPIV3 N gene stop/N gene start sequences.

Figure 5. b/h PIV3 vectored RSV F or G gene displayed a positional effect. (A) is a Western blot analysis of chimeric virus-infected cell lysates. F protein was detected using monoclonal antibodies (MAbs) against the RSV F protein, and G protein was detected using polyclonal antibodies (PAbs) against the RSV G protein. A 50 kDa band representing the F₁ fragment was detected in cells infected with all chimeric viruses as well as wild-type RSV.
10 There was a greater accumulation of a 20 kDa F fragment in infected cell lysates of chimeric viruses compared to wild-type RSV. The experiment was done at MOI of 0.1, except that in lane 1, b/h PIV3 vectored RSV F1* N-N infections were repeated at a higher MOI of 1.0.
15 Both the immature and glycosylated forms of RSV G protein that migrated at approximately 50 kDa and 90 kDa were detected. (B) is a Northern blot analysis, which showed that the mRNA transcription correlated with the result of the protein expression demonstrated in Figure 5A. Equal amounts of total RNA were separated on 1% agarose gels containing 1% formaldehyde and transferred to nylon membranes. The blots were hybridized with
20 digoxigenin (DIG)-UTP-labeled riboprobes synthesized by in vitro transcription using a DIG RNA labeling kit. (C) is growth curves of chimeric viruses comprising b/h PIV3 vectored RSV F or G protein in Vero cells. Vero cells were grown to 90% confluence and infected at an MOI of 0.01. The infected monolayers were incubated at 37°C. Virus titers for each time point harvest were determined by TCID₅₀ assays, which were performed by inspecting
25 visually for CPE following incubation at 37°C for 6 days.

Figure 6. The b/h PIV3 vectored enhanced green fluorescence protein (eGFP) constructs. The eGFP gene is introduced into the b/h PIV3 vector sequentially between all genes of PIV3 (only position 1, 2, 3, and 4 are shown here). The eGFP gene was linked to the bPIV3 N-P intergenic region. The b/h GFP 1 construct harbors the eGFP gene cassette in the 3' most proximal position of the b/h PIV3 genome. The b/h GFP 2 construct contains
30

the eGFP gene cassette between the N and P genes. The b/h GFP 3 construct contains the eGFP gene cassette between the P and M gene, and the b/h GFP4 construct contains the eGFP gene between M and F of b/h PIV3.

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Figure 7. Positional effect of enhanced green fluorescence protein (eGFP) insertions in the b/h PIV3 genome. (A) shows the amount of green cells produced upon infecting Vero cells with b/h PIV3 vectored eGFP 1, 2, and 3 at MOI 0.1 and MOI 0.01 for 20 hours. The green cells were visualized by using a fluorescent microscope. (B) is a Western blot analysis 10 of infected cell lysates. The blots were probed with a GFP MAb as well as a PIV3 PAb. PIV3 antibody was also used to show that the blots had same volume loading. (C) is growth curves of b/h PIV3 vectored GFP constructs (at position 1, 2, and 3) in Vero cells.

15

Figure 8. Constructs of b/h PIV3 vectored RSV F gene with different intergenic regions. The three constructs, RSV F1* N-N, RSV F2 N-P, and RSV F1 N-P are the same as the RSV F* (N-N), RSV F2, and RSV F1 in Figure 4 respectively. The distance between the N gene start sequence and the N gene translation start codon in RSV F1* N-N is only 10 nucleotides (nts) long. In contrast, this distance is 86 nts long in RSV F2 construct. RSV F1* N-N also uses the N gene start sequence rather than the P gene start sequence as is done 20 in RSV F2 construct.

25

Figure 9. The length and/or nature of the intergenic region downstream of the inserted RSV gene has an effect on virus replication. (A) Western blot analysis of RSV F protein expression in chimeric viruses. Blots were probed with monoclonal antibodies against the RSV F protein. F1 protein levels expressed by RSV F1 construct and measured at 24 and 48 hours post-infection were close to the levels observed for RSV F2 construct, but much higher than those of RSV F1* N-N construct. (B) is multicycle growth curves comparing the kinetics of virus replication of RSV F1, RSV F1*N-N and RSV F2 constructs in Vero cells at an MOI of 0.1. Virus titers for each time point harvest were determined by 30 plaque assays, which were performed by immunostaining with RSV polyclonal antisera for quantification after 5 days of incubation.

Figure 10. Constructs of trivalent b/h PIV3 vectored RSV F and hMPV F. Two virus genomes, each comprising a chimeric b/h PIV3 vector and a first heterologous sequences derived from a metapneumovirus F gene and a second heterologous sequence derived from respiratory syncytial virus F gene, are shown here. Virus with either of the constructs has been amplified in Vero cells. The engineered virus as described can be used as a trivalent vaccine against the parainfluenza virus infection, metapneumovirus infection and the respiratory syncytial virus infection.

Figure 11. A construct harboring two RSV F genes. This construct can be used to determine virus growth kinetics, for RSV F protein production, and replication and immunogenicity in hamsters.

Figure 12. The chimeric b/h PIV3 vectored hMPV F constructs. The F gene of human metapneumovirus (hMPV) was inserted in position 1 or position 2 of the b/h PIV3 genome. The hMPV F gene cassette harbored the bPIV3 N-P intergenic region.

Figure 13. Immunoprecipitation and replication assays of b/h PIV3 vectored hMPV F gene (at position 2). (A) shows the immunoprecipitation of hMPV F protein using guinea pig or human anti-hMPV antiserum. A specific band migrating at approximately 80 kDa was observed in the lysates of b/h PIV3 vectored hMPV F2. This size corresponds to the F precursor protein, F₀. Non-specific bands of different sizes were also observed in the b/h PIV3 and mock control lanes. (B) shows growth curves that were performed to determine the kinetics of virus replication of b/h PIV3/hMPV F2 and compare it to those observed for b/h PIV3 and b/h PIV3/RSV F2 in Vero cells at an MOI of 0.1. (C) is growth curves that were performed to determine the kinetics of virus replication of b/h PIV3/hMPV F1 and compare it to those observed for b/h PIV3/hMPV F2 and b/h PIV3 in Vero cells at an MOI of 0.01.

Figure 14. A chimeric b/h PIV3 vectored soluble RSV F gene construct. This construct comprises a single copy of the soluble RSV F gene, a version of the RSV F gene

lacking the transmembrane and cytosolic domains. The advantage of this construct would be the inability of the soluble RSV F to be incorporated into the virion genome.

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Figure 15. Immunostained b/h PIV3/hMPV F1 and b/h PIV3/hMPV F2. (A) the b/h PIV3/hMPV F1 virus were diluted and used to infect subconfluent Vero cells. Infected cells were overlayed with optiMEM media containing gentamycin and incubated at 35°C for 5 days. Cells were fixed and immunostained with guinea pig anti-hMPV sera. Expression of hMPV F is visualized by specific color development in the presence of the AEC substrate system. (B) the b/h PIV3/hMPV F2 virus were diluted and used to infect Vero cells. Infected cells were overlayed with 1% methyl cellulose in EMEM/L-15 medium (JRH Biosciences; Lenexa, KS). Cells were incubated, fixed and then immunostained with anti-hMPV guinea pig sera. The anti-hMPV guinea pig serum is specific for hMPV 001 protein.

15

Figure 16. Virion fractionation of b/h PIV3 vectored RSV genes on sucrose gradients. These series experiments investigate whether the RSV proteins were incorporated into the b/h PIV3 virion. (A) shows control gradient of free RSV F (generated in baculovirus and C-terminally truncated). Majority of free RSV F was present in fractions 3, 4, 5, and 6. (B) shows that the biggest concentration of RSV virions was observed in fractions 10, 11 and 12. The RSV fractions were probed with RSV polyclonal antiserum as well as RSV F MAb. The fractions that contained the greatest amounts of RSV virions also showed the strongest signal for RSV F, suggesting that the RSV F protein co-migrated and associated with RSV virion. The last figure on (B) also shows that the fractions 10, 11 and 12 displayed the highest virus titer by plaque assay. (C) The b/h PIV3 virions may be more pleiomorphic and thus the spread of the peak fractions containing b/h PIV3 virions was more broad. (D) Sucrose gradient fractions of b/h PIV3/RSV F2 were analyzed with both a PIV polyclonal antiserum and an RSV F MAb. The fractions containing most of the virions were fractions 11, 12, 13 and 14, as shown by Western using the PIV3 antiserum.

20

Correspondingly, these were also the fractions that displayed the highest amounts of RSV F protein. Some free RSV F was also present in fractions 5 and 6. Fractions 11, 12, 13 and 14 displayed the peak virus titers. (E) The fractions containing the most virions of b/h

PIV3/RSV G2 (9, 10, 11 and 12) also showed the strongest signal for RSV G protein. Again, these were the fractions with the highest virus titers.

5

5. DESCRIPTION OF THE INVENTION

The present invention relates to recombinant parainfluenza cDNA and RNA constructs, including but not limited to, recombinant bovine and human PIV cDNA and RNA constructs, that may be used to express heterologous or non-native sequences.

In accordance with the present invention, a recombinant virus is one derived from a 10 bovine parainfluenza virus or a human parainfluenza virus that is encoded by endogenous or native genomic sequences or non-native genomic sequences. In accordance with the invention, a non-native sequence is one that is different from the native or endogenous genomic sequence due to one or more mutations, including, but not limited to, point 15 mutations, rearrangements, insertions, deletions, etc. to the genomic sequence that may or may not result in a phenotypic change.

In accordance with the present invention, a chimeric virus of the invention is a recombinant bPIV or hPIV which further comprises one or more heterologous nucleotide 20 sequences. In accordance with the invention, a chimeric virus may be encoded by a nucleotide sequence in which heterologous nucleotide sequences have been added to the genome or in which nucleotide sequences have been replaced with heterologous nucleotide sequences. These recombinant and chimeric viruses and expression products may be used as vaccines suitable for administration to humans or animals. For example, the chimeric 25 viruses of the invention may be used in vaccine formulations to confer protection against pneumovirus, respiratory syncytial virus, parainfluenza virus, or influenza virus infection.

In one embodiment, the invention relates to PIV cDNA and RNA constructs that are derived from human or bovine PIV variants and are engineered to express one, two, or three 30 heterologous sequences, preferably heterologous genes encoding foreign antigens and other products from a variety of pathogens, cellular genes, tumor antigens, and viruses. In particular, the heterologous sequences are derived from morbillivirus or a negative strand RNA virus, including but not limited to, influenza virus, respiratory syncytial virus (RSV), mammalian metapneumovirus (e.g., human metapneumovirus variants A1, A2, B1, and B2),

and avian pneumovirus subgroups A, B, C and D. The mammalian MPVs can be a variant A1, A2, B1 or B2 mammalian MPV. However, the mammalian MPVs of the present invention may encompass additional variants of MPV yet to be identified, and are not limited to variants A1, A2, B1, or B2. In another embodiment of the invention, the heterologous sequences are non-native PIV sequences, including mutated PIV sequences. In some embodiments, the heterologous sequences are derived from the same or from different viruses.

In a specific embodiment, the virus of the invention is a recombinant PIV comprising heterologous nucleotide sequences derived from human metapneumovirus or avian pneumovirus. The heterologous sequences to be inserted into the PIV genome include, but are not limited to, the sequences encoding the F, G and HN genes of human metapneumovirus variants A1, A2, B1 or B2, sequences encoding the F, G and HN genes of avian pneumovirus type A, B, C or D, and immunogenic and/or antigenic fragments thereof.

In certain embodiments, the heterologous nucleotide sequence is added to the viral genome. In alternative embodiments, the heterologous nucleotide sequence is exchanged for an endogenous nucleotide sequence. The heterologous nucleotide sequence may be added or inserted at various positions of the PIV genome, e.g., at position 1, 2, 3, 4, 5, or 6. In a preferred embodiment, the heterologous nucleotide sequence is added or inserted at position

1. In another preferred embodiment, the heterologous nucleotide sequence is added or inserted at position 2. In even another preferred embodiment, the heterologous nucleotide sequence is added or inserted at position 3. Inserting or adding heterologous nucleotide sequences at the lower-numbered positions of the virus generally results in stronger expression of the heterologous nucleotide sequence compared to insertion at higher-numbered positions. This is due to a transcriptional gradient that occurs across the genome of the virus. However, virus replication efficiency must also be considered. For example, in the b/h PIV3 chimeric virus of the invention, insertion of a heterologous gene at position 1 delays replication kinetics *in vitro* and to a lesser degree also *in vivo* (see section 8, example 3 and Figure 5 as well as section 26, example 21). Therefore, inserting heterologous nucleotide sequences at lower-numbered positions is the preferred embodiment of the invention if strong expression of the heterologous nucleotide sequence is desired. Most

preferably, a heterologous sequence is inserted at position 2 of a b/h PIV3 genome if strong expression of the heterologous sequence is desired. (See section 5.1.2. *infra* and section 8, example 3).

5 In some other embodiments, the recombinant or chimeric PIV genome is engineered such that the intergenic region between the end of the coding sequence of the heterologous gene and the start of the coding sequence of the downstream gene is altered. In yet some other embodiments, the virus of the invention comprises a recombinant or chimeric PIV genome engineered such that the heterologous nucleotide sequence is inserted at a position
10 selected from the group consisting of positions 1, 2, 3, 4, 5, and 6, and the intergenic region between the heterologous nucleotide sequence and the next downstream gene is altered. Appropriate assays may be used to determine the best mode of insertion (*i.e.*, which position to insert, and the length of the intergenic region) to achieve appropriate levels of gene expression and viral growth characteristics. For detail, *see* Section 5.1.2., *infra*.

15 In certain embodiments, the chimeric virus of the invention contains two different heterologous nucleotide sequences. The different heterologous nucleotide sequences may be inserted at various positions of the PIV genome. In a preferred embodiment, one heterologous nucleotide sequence is inserted at position 1 and another heterologous nucleotide sequence is added or inserted at position 2 or 3. In other embodiments of the
20 invention, additional heterologous nucleotide sequences are inserted at higher-numbered positions of the PIV genome. In accordance with the present invention, the position of the heterologous sequence refers to the order in which the sequences are transcribed from the viral genome, *e.g.*, a heterologous sequence at position 1 is the first gene sequence to be transcribed from the genome.

25 In certain embodiments of the invention, the heterologous nucleotide sequence to be inserted into the genome of the virus of the invention is derived from a negative strand RNA virus, including but not limited to, influenza virus, parainfluenza virus, respiratory syncytial virus, mammalian metapneumovirus, and avian pneumovirus. In a specific embodiment of the invention, the heterologous nucleotide sequence is derived from a human
30 metapneumovirus. In another specific embodiment, the heterologous nucleotide sequence is

derived from an avian pneumovirus. More specifically, the heterologous nucleotide sequence of the invention encodes a F, G or SH gene or a portion thereof of a human or avian metapneumovirus. In specific embodiments, a heterologous nucleotide sequences can be any one of SEQ ID NO:1 through SEQ ID NO:5, SEQ ID NO:14, and SEQ ID NO:15 (see Table 16). In certain specific embodiments, the nucleotide sequence encodes a protein of any one of SEQ ID NO:6 through SEQ ID NO:13, SEQ ID NO:16, and SEQ ID NO:17 (see Table 16). In certain specific embodiments, the nucleotide sequence encodes a protein of any one of SEQ ID NO: 314 through 389.

10 In specific embodiments of the invention, a heterologous nucleotide sequence of the invention is derived from a type A avian pneumovirus. In other specific embodiments of the invention, a heterologous nucleotide sequence of the invention is derived from a type B avian pneumovirus. In even other specific embodiments of the invention, a heterologous nucleotide sequence of the invention is derived from a type C avian pneumovirus.

15 Phylogenetic analyses show that type A and type B are more closely related to each other than they are to type C (Seal, 2000, Animal Health Res. Rev. 1(1):67-72). Type A and type B are found in Europe whereas type C was first isolated in the U.S.

20 In another embodiment of the invention, the heterologous nucleotide sequence encodes a chimeric polypeptide, wherein the ectodomain contains antigenic sequences derived from a virus other than the strain of PIV from which the vector backbone is derived, and the trans membrane and luminal domains are derived from PIV sequences. The resulting chimeric virus would impart antigenicity of the negative strand RNA virus of choice and would have an attenuated phenotype.

25 In a specific embodiment of the invention, the heterologous nucleotide sequence encodes a chimeric F protein. Particularly, the ectodomain of the chimeric F protein is the ectodomain of a metapneumovirus, so that a human metapneumovirus or avian pneumovirus, and the transmembrane domain as well as the luminal domain are the transmembrane and luminal domains of a parainfluenza virus, such as a human or a bovine parainfluenza virus. While not bound by any theory, insertion of a chimeric F protein may further attenuate the 30 virus in an intended host but retain the antigenicity of the F protein attributed by its ectodomain.

The chimeric viruses of the invention may be used in vaccine formulations to confer protection against various infections, including but not limited to, pneumovirus infection, respiratory syncytial virus infection, parainfluenza virus infection, influenza virus infection, or a combination thereof. The present invention provides vaccine preparations comprising chimeric PIV expressing one or more heterologous antigenic sequences, including bivalent and trivalent vaccines. The bivalent and trivalent vaccines of the invention may be administered in the form of one PIV vector expressing each heterologous antigenic sequences or two or more PIV vectors each encoding different heterologous antigenic sequences.

5 Preferably, the heterologous antigenic sequences are derived from a negative strand RNA virus, including but not limited to, influenza virus, parainfluenza virus, respiratory syncytial virus (RSV), mammalian metapneumovirus (*e.g.*, human metapneumovirus) and avian pneumovirus. Thus, the chimeric virions of the present invention may be engineered to create, *e.g.*, anti-human influenza vaccine, anti-human parainfluenza vaccine, anti-human

10 RSV vaccine, and anti-human metapneumovirus vaccine. Preferably, the vaccine preparation of the invention comprises attenuated chimeric viruses that are viable and infectious. The vaccine preparation of the invention can be administered alone or in combination with other vaccines or other prophylactic or therapeutic agents.

15

The present invention also relates to the use of viral vectors and chimeric viruses to formulate vaccines against a broad range of viruses and/or antigens including tumor antigens. The viral vectors and chimeric viruses of the present invention may be used to modulate a subject's immune system by stimulating a humoral immune response, a cellular immune response or by stimulating tolerance to an antigen. As used herein, a subject refers to a human, a primate, a horse, a cow, a sheep, a pig, a goat, a dog, a cat, a rodent and a member

20 of avian species. When delivering tumor antigens, the invention may be used to treat subjects having disease amenable to immune response mediated rejection, such as non-solid tumors or solid tumors of small size. It is also contemplated that delivery of tumor antigens by the viral vectors and chimeric viruses described herein will be useful for treatment

25 subsequent to removal of large solid tumors. The invention may also be used to treat subjects who are suspected of having cancer.

30

The invention may be divided into the following stages solely for the purpose of description and not by way of limitation: (a) construction of recombinant cDNA and RNA templates; (b) expression of heterologous gene products using recombinant cDNA and RNA templates; and (c) rescue of the heterologous genes in recombinant virus particles.

5.1. CONSTRUCTION OF THE RECOMBINANT cDNA AND RNA

The present invention encompasses recombinant or chimeric viruses encoded by viral vectors derived from the genomes of parainfluenza virus, including both bovine 10 parainfluenza virus and mammalian parainfluenza virus. In accordance with the present invention, a recombinant virus is one derived from a bovine parainfluenza virus or a mammalian parainfluenza virus that is encoded by endogenous or native genomic sequences or non-native genomic sequences. In accordance with the invention, a non-native sequence is one that is different from the native or endogenous genomic sequence due to one or more 15 mutations, including, but not limited to, point mutations, rearrangements, insertions, deletions etc. to the genomic sequence that may or may not result a phenotypic change. The recombinant viruses of the invention encompass those viruses encoded by viral vectors derived from the genomes of parainfluenza virus, including both bovine and mammalian parainfluenza virus, and may or may not, include nucleic acids that are non-native to the viral 20 genome. In accordance with the present invention, a viral vector which is derived from the genome of a parainfluenza virus is one that contains a nucleic acid sequence that encodes at least a part of one ORF of a parainfluenza virus.

The present invention also encompasses recombinant viruses comprising a viral vector derived from a bovine and/or mammalian PIV genome which contains sequences 25 which result in a virus having a phenotype more suitable for use in vaccine formulations, e.g., attenuated phenotype or enhanced antigenicity. The mutations and modifications can be in coding regions, in intergenic regions and in the leader and trailer sequences of the virus.

In accordance with the present invention, the viral vectors of the invention are derived from the genome of a mammalian parainfluenza virus, in particular a human parainfluenza 30 virus (hPIV). In particular embodiments of the invention, the viral vector is derived from the genome of a human parainfluenza virus type 3. In accordance with the present invention,

these viral vectors may or may not include nucleic acids that are non-native to the viral genome.

5 In accordance with the present invention, the viral vectors of the inventions are derived from the genome of a bovine parainfluenza virus (bPIV). In particular embodiments of the invention, the viral vector is derived from the genome of bovine parainfluenza virus type 3. In accordance to the present invention, these viral vectors may or may include nucleic acids that are non-native to the viral genome.

10 In accordance with the invention, a chimeric virus is a recombinant bPIV or hPIV which further comprises a heterologous nucleotide sequence. In accordance with the invention, a chimeric virus may be encoded by a nucleotide sequence in which heterologous nucleotide sequence have been added to the genome or in which endogenous or native nucleotide sequence have been replaced with heterologous nucleotide sequence. In accordance with the invention, the chimeric viruses are encoded by the viral vectors of the invention which further comprise a heterologous nucleotide sequence. In accordance with the present invention, a chimeric virus is encoded by a viral vector that may or may not include nucleic acids that are non-native to the viral genome. In accordance with the invention, a chimeric virus is encoded by a viral vector to which heterologous nucleotide sequences have been added, inserted or substituted for native or non-native sequences.

15

20 A chimeric virus may be of particular use for the generation of recombinant vaccines protecting against two or more viruses (Tao et al., J. Virol. 72, 2955-2961; Durbin et al., 2000, J. Virol. 74, 6821-6831; Skiadopoulos et al., 1998, J. Virol. 72, 1762-1768 (1998); Teng et al., 2000, J. Virol. 74, 9317-9321). For example, it can be envisaged that a hPIV or bPIV virus vector expressing one or more proteins of another negative strand RNA virus, e.g., MPV, or a RSV vector expressing one or more proteins of MPV will protect individuals vaccinated with such vector against both virus infections. A similar approach can be envisaged for other paramyxoviruses. Attenuated and replication-defective viruses may be of use for vaccination purposes with live vaccines as has been suggested for other viruses. (See, PCT WO 02/057302, at pp. 6 and 23, incorporated by reference herein).

25

30 In accordance with the present invention the heterologous to be incorporated into the viral vectors encoding the recombinant or chimeric viruses of the invention include

sequences obtained or derived from different strains of metapneumovirus, strains of avian pneumovirus, and other negative strand RNA viruses, including, but not limited to, RSV, PIV, influenza virus and other viruses, including morbillivirus.

5 In certain embodiments of the invention, the chimeric or recombinant viruses of the invention are encoded by viral vectors derived from viral genomes wherein one or more sequences, intergenic regions, termini sequences, or portions or entire ORF have been substituted with a heterologous or non-native sequence. In certain embodiments of the invention, the chimeric viruses of the invention are encoded by viral vectors derived from
10 viral genomes wherein one or more heterologous sequences have been added to the vector.

A specific embodiment of the present invention is a chimeric virus comprising a backbone encoded by nucleotide sequences derived from a parainfluenza virus genome. In a preferred embodiment, the PIV genome is derived from bovine PIV, such as the Kansas strain of bPIV3, or from human PIV. In a preferred embodiment, the PIV genome is derived
15 from the Kansas strain of bPIV3, in which bovine parainfluenza virus nucleotide sequences have been substituted with heterologous sequences or in which heterologous sequences have been added to the complete bPIV genome. A further specific embodiment of the present invention is a chimeric virus comprising a backbone encoded by nucleotide sequences derived from human parainfluenza virus type 3 genome, in which human parainfluenza virus
20 nucleotide sequences have been substituted with heterologous sequences or in which heterologous sequences have been added to the complete hPIV genome. An additional specific embodiment of the present invention is a chimeric virus comprising a backbone encoded by nucleotide sequences derived from bovine parainfluenza virus genome, such as the Kansas strain of bPIV3, in which (a) the bovine parainfluenza virus F gene and HN gene
25 have been substituted with the F gene and the HN gene of the human parainfluenza virus (bPIV/hPIV), and in which (b) heterologous sequences have been added to the complete bPIV genome.

The present invention also encompasses chimeric viruses comprising a backbone encoded by nucleotide sequences derived from the bPIV, the hPIV, or the bPIV/hPIV
30 genome containing mutations or modifications, in addition to heterologous sequences, that result in a chimeric virus having a phenotype more suitable for use in vaccine formulations,

e.g., attenuated phenotype or enhanced antigenicity. In accordance with this particular embodiment of the invention, a heterologous sequence in the context of a bovine PIV3 backbone may be any sequence heterologous to bPIV3.

5 Another specific embodiment of the present invention is a chimeric virus comprising a backbone encoded by nucleotide sequences derived from human PIV 1, 2, or 3 in which hPIV nucleotide sequences have been substituted with heterologous sequences or in which heterologous sequences have been added to the complete hPIV genome, with the proviso that the resulting chimeric virus is not a chimeric hPIV3 in which the hemagglutinin-
10 neuraminidase and fusion glycoproteins have been replaced by those of hPIV1. The present invention also encompasses chimeric viruses, comprising a backbone encoded by nucleotide sequences derived from a hPIV genome, containing mutations or modifications, in addition to heterologous sequences, that result in a chimeric virus having a phenotype more suitable for use in vaccine formulations, e.g., attenuated phenotype or enhanced antigenicity.
15

Heterologous gene coding sequences flanked by the complement of the viral polymerase binding site/promoter, e.g., the complement of 3'-PIV virus terminus of the present invention, or the complements of both the 3'- and 5'-PIV virus termini may be constructed using techniques known in the art. The resulting RNA templates may be of the negative-polarity and can contain appropriate terminal sequences that enable the viral RNA-
20 synthesizing apparatus to recognize the template. Alternatively, positive-polarity RNA templates, that contain appropriate terminal sequences which enable the viral RNA-synthesizing apparatus to recognize the template, may also be used. Recombinant DNA molecules containing these hybrid sequences can be cloned and transcribed by a DNA-directed RNA polymerase, such as bacteriophage T7 polymerase, T3 polymerase, the SP6
25 polymerase or a eukaryotic polymerase such as polymerase I and the like, for the *in vitro* or *in vivo* production of recombinant RNA templates that possess the appropriate viral sequences and that allow for viral polymerase recognition and activity.

In one embodiment, the PIV vector of the invention expresses one, two, or three heterologous sequences, encoding antigenic polypeptides and peptides. In some
30 embodiments, the heterologous sequences are derived from the same virus or from different viruses. In certain embodiments, more than one copy of the same heterologous nucleotide

sequences are inserted in the genome of a bovine parainfluenza virus, human parainfluenza virus, or bPIV/hPIV chimeric vector. In a preferred embodiment, two copies of the same heterologous nucleotide sequences are inserted to the genome of the virus of the invention.

5 In some embodiments, the heterologous nucleotide sequence is derived from a metapneumovirus, such as human metapneumovirus or an avian pneumovirus. In specific embodiments, the heterologous nucleotide sequence derived from a metapneumovirus is a F gene of the metapneumovirus. In other specific embodiments, the heterologous nucleotide sequence derived from a metapneumovirus is a G gene of the metapneumovirus. In some
10 other embodiments, the heterologous nucleotide sequence is derived from a respiratory syncytial virus. In specific embodiments, the heterologous nucleotide sequence derived from respiratory syncytial virus is a F gene of the respiratory syncytial virus. In other specific embodiments, the heterologous nucleotide sequence derived from respiratory syncytial virus is a G gene of the respiratory syncytial virus. When one or more heterologous nucleotide
15 sequences are inserted, the position of the insertion and the length of the intergenic region of each inserted copy can be manipulated and determined by different assays according to section 5.1.2. *infra*.

In certain embodiments, rescue of the chimeric virus or expression products may be achieved by reverse genetics in host cell systems where the host cells are transfected with
20 chimeric cDNA or RNA constructs. The RNA templates of the present invention are prepared by transcription of appropriate DNA sequences with a DNA-directed RNA polymerase. The RNA templates of the present invention may be prepared either *in vitro* or *in vivo* by transcription of appropriate DNA sequences using a DNA-directed RNA polymerase such as bacteriophage T7 polymerase, T3 polymerase, the SP6 polymerase, or a
25 eukaryotic polymerase such as polymerase I. In certain embodiments, the RNA templates of the present invention may be prepared either *in vitro* or *in vivo* by transcription of appropriate DNA sequences using a plasmid-based expression system as described in Hoffmann *et al.*, 2000, Proc. Natl. Acad. Sci. USA 97:6108-6113 or the unidirectional RNA polymerase I-polymerase II transcription system as described in Hoffmann and Webster, 2000, J. Gen.
30 Virol. 81:2843-2847. The resulting RNA templates of negative-polarity would contain appropriate terminal sequences that would enable the viral RNA-synthesizing apparatus to

5 recognize the template. Alternatively, positive-polarity RNA templates that contain appropriate terminal sequences and enable the viral RNA-synthesizing apparatus to recognize the template may also be used. Expression from positive polarity RNA templates may be achieved by transfection of plasmids having promoters that are recognized by the DNA-dependent RNA polymerase. For example, plasmid DNA, encoding positive RNA templates under the control of a T7 promoter, can be used in combination with the vaccinia virus or fowlpox T7 system.

10 Bicistronic mRNAs can be constructed to permit internal initiation of translation of viral sequences and to allow for the expression of foreign protein coding sequences from the regular terminal initiation site, or vice versa. Alternatively, a foreign protein may be expressed from an internal transcriptional unit in which the transcriptional unit has an initiation site and polyadenylation site. In another embodiment, the foreign gene is inserted into a PIV gene such that the resulting expressed protein is a fusion protein.

15 20 25 30 In certain embodiments, the invention relates to trivalent vaccines comprising a virus of the invention. In specific embodiments, the virus used for a trivalent vaccine is a chimeric bovine parainfluenza type 3/human parainfluenza type3 virus containing a first heterologous nucleotide sequence derived from a metapneumovirus, such as human metapneumovirus or avian pneumovirus, and a second heterologous nucleotide sequence derived from respiratory syncytial virus. In an exemplary embodiment, such a trivalent vaccine would be specific to (a) the gene products of the F gene and the HN gene of the human parainfluenza virus; (b) the protein encoded by the heterologous nucleotide sequence derived from a metapneumovirus; and ©) the protein encoded by the heterologous nucleotide sequence derived from a respiratory syncytial virus. In a specific embodiment, the first heterologous nucleotide sequence is the F gene of the respiratory syncytial virus and is inserted in position 1, and the second heterologous nucleotide sequence is the F gene of the human metapneumovirus and is inserted in position 3. Many more combinations are encompassed by the present invention and some are shown by way of example in Table 1. For other combinations the F or G gene of an avian pneumovirus could be used. Further, nucleotide sequences encoding chimeric F proteins could be used (see *supra*). In some less preferred

embodiments, the heterologous nucleotide sequence can be inserted at higher-numbered positions of the viral genome.

5

Table 1. Exemplary arrangements of heterologous nucleotide sequences in the viruses used for trivalent vaccines.

	<u>Combination</u>	<u>Position 1</u>	<u>Position 2</u>	<u>Position 3</u>
	1	F-gene of hMPV	F-gene of RSV	-
10	2	F-gene of RSV	F-gene of hMPV	-
	3	-	F-gene of hMPV	F-gene of RSV
	4	-	F-gene of RSV	F-gene of hMPV
	5	F-gene of hMPV	-	F-gene of RSV
	6	F-gene of RSV	-	F-gene of hMPV
	7	G-gene of hMPV	G-gene of RSV	-
	8	G-gene of RSV	G-gene of hMPV	-
	9	-	G-gene of hMPV	G-gene of RSV
	10	-	G-gene of RSV	G-gene of hMPV
15	11	G-gene of hMPV	-	G-gene of RSV
	12	G-gene of RSV	-	G-gene of hMPV
	13	F-gene of hMPV	G-gene of RSV	-
	14	G-gene of RSV	F-gene of hMPV	-
	15	-	F-gene of hMPV	G-gene of RSV
	16	-	G-gene of RSV	F-gene of hMPV
	17	F-gene of hMPV	-	G-gene of RSV
	18	G-gene of RSV	-	F-gene of hMPV
	19	G-gene of hMPV	F-gene of RSV	-
20	20	F-gene of RSV	G-gene of hMPV	-
	21	-	G-gene of hMPV	F-gene of RSV
	22	-	F-gene of RSV	G-gene of hMPV
	23	G-gene of hMPV	-	F-gene of RSV
	24	F-gene of RSV	-	G-gene of hMPV

In some other embodiments, the intergenic region between a heterologous sequence and the start of the coding sequence of the downstream gene can be altered. For example, each gene listed on Table 1 may have a desirable length of the intergenic region. In an exemplary embodiment, a trivalent vaccine comprises a b/h PIV3 vector with a F gene of respiratory syncytial virus inserted at position 1, an altered intergenic region of 177 nucleotides (originally 75 nucleotides to the downstream N gene start codon AUG), and a F gene of human metapneumovirus inserted at position 3 with its natural intergenic region.

Many more combinations are encompassed by the present invention, as each insertion of a heterologous nucleotide sequence may be manipulated according to section 5.1.2., *infra*.

In a broader embodiment, the expression products and chimeric virions of the present
5 invention may be engineered to create vaccines against a broad range of pathogens, including viral antigens, tumor antigens and auto antigens involved in autoimmune disorders. One way to achieve this goal involves modifying existing PIV genes to contain foreign sequences in their respective external domains. Where the heterologous sequences are epitopes or
10 antigens of pathogens, these chimeric viruses may be used to induce a protective immune response against the disease agent from which these determinants are derived.

One approach for constructing these hybrid molecules is to insert the heterologous nucleotide sequence into a DNA complement of a PIV genome, *e.g.*, a hPIV, a bPIV, or a
15 bPIV/hPIV, so that the heterologous sequence is flanked by the viral sequences required for viral polymerase activity; *i.e.*, the viral polymerase binding site/promoter, hereinafter referred to as the viral polymerase binding site, and a polyadenylation site. In a preferred embodiment, the heterologous coding sequence is flanked by the viral sequences that comprise the replication promoters of the 5' and 3' termini, the gene start and gene end sequences, and the packaging signals that are found in the 5' and/or the 3' termini. In an alternative approach, oligonucleotides encoding the viral polymerase binding site, *e.g.*, the
20 complement of the 3'-terminus or both termini of the virus genomic segment can be ligated to the heterologous coding sequence to construct the hybrid molecule. The placement of a foreign gene or segment of a foreign gene within a target sequence was formerly dictated by the presence of appropriate restriction enzyme sites within the target sequence. However,
25 recent advances in molecular biology have lessened this problem greatly. Restriction enzyme sites can readily be placed anywhere within a target sequence through the use of site-directed mutagenesis (*e.g.*, see, for example, the techniques described by Kunkel, 1985, Proc. Natl. Acad. Sci. U.S.A. 82:488). Variations in polymerase chain reaction (PCR) technology, described *infra*, also allow for the specific insertion of sequences (*i.e.*, restriction enzyme sites) and also allow for the facile construction of hybrid molecules. Alternatively, PCR
30 reactions could be used to prepare recombinant templates without the need of cloning. For example, PCR reactions could be used to prepare double-stranded DNA molecules

containing a DNA-directed RNA polymerase promoter (e.g., bacteriophage T3, T7 or SP6) and the hybrid sequence containing the heterologous gene and the PIV polymerase binding site. RNA templates could then be transcribed directly from this recombinant DNA. In yet
5 another embodiment, the recombinant RNA templates may be prepared by ligating RNAs specifying the negative polarity of the heterologous gene and the viral polymerase binding site using an RNA ligase.

In addition, one or more nucleotides can be added at the 3' end of the HN gene in the untranslated region to adhere to the "Rule of Six" which may be important in successful virus
10 rescue. The "Rule of Six" applies to many paramyxoviruses and requires that the number of nucleotides of an RNA genome be a factor of six to be functional. The addition of nucleotides can be accomplished by techniques known in the art such as using a commercial mutagenesis kits like the QuikChange mutagenesis kit (Stratagene). After addition of the appropriate number of nucleotides, the correct DNA fragment, for example, a DNA fragment
15 of the hPIV3 F and HN gene, can then be isolated upon digestion with the appropriate restriction enzyme and gel purification. Sequence requirements for viral polymerase activity and constructs that may be used in accordance with the invention are described in the subsections below.

Without being bound by theory, several parameters affect the rate of replication of the
20 recombinant virus and the level of expression of the heterologous sequence. In particular, the position of the heterologous sequence in bPIV, hPIV, b/h PIV and the length of the intergenic region that flanks the heterologous sequence determine rate of replication and expression level of the heterologous sequence.

In certain embodiments, the leader and/or trailer sequence of the virus are modified
25 relative to the wild type virus. In certain more specific embodiments, the lengths of the leader and/or trailer are altered. In other embodiments, the sequence(s) of the leader and/or trailer are mutated relative to the wild type virus.

The production of a recombinant virus of the invention relies on the replication of a partial or full-length copy of the negative sense viral RNA (vRNA) genome or a
30 complementary copy thereof (cRNA). This vRNA or cRNA can be isolated from infectious virus, produced upon in-vitro transcription, or produced in cells upon transfection of nucleic

acids. Second, the production of recombinant negative strand virus relies on a functional polymerase complex. Typically, the polymerase complex of pneumoviruses consists of N, P, L and possibly M2 proteins, but is not necessarily limited thereto.

5 Polymerase complexes or components thereof can be isolated from virus particles, isolated from cells expressing one or more of the components, or produced upon transfection of specific expression vectors.

Infectious copies of MPV can be obtained when the above mentioned vRNA, cRNA, or vectors expressing these RNAs are replicated by the above mentioned polymerase 10 complex 16 (Schnell *et al.*, 1994, EMBO J 13: 4195-4203; Collins *et al.*, 1995, PNAS 92: 11563-11567; Hoffmann *et al.*, 2000, PNAS 97: 6108-6113; Bridgen *et al.*, 1996, PNAS 93: 15400-15404; Palese *et al.*, 1996, PNAS 93: 11354-11358; Peeters *et al.*, 1999, J.Virol. 73: 5001-5009; Durbin *et al.*, 1997, Virology 235: 323-332).

The invention provides a host cell comprising a nucleic acid or a vector according to 15 the invention. Plasmid or viral vectors containing the polymerase components of PIV (presumably N, P, L and M2, but not necessarily limited thereto) are generated in prokaryotic cells for the expression of the components in relevant cell types (bacteria, insect cells, eukaryotic cells). Plasmid or viral vectors containing full-length or partial copies of the PIV genome will be generated in prokaryotic cells for the expression of viral nucleic acids *in vitro* 20 or *in vivo*. The latter vectors may contain other viral sequences for the generation of chimeric viruses or chimeric virus proteins, may lack parts of the viral genome for the generation of replication defective virus, and may contain mutations, deletions or insertions for the generation of attenuated viruses.

Infectious copies of PIV (being wild type, attenuated, replication-defective or 25 chimeric) can be produced upon co-expression of the polymerase components according to the state-of-the-art technologies described above.

In addition, eukaryotic cells, transiently or stably expressing one or more full-length or partial PIV proteins can be used. Such cells can be made by transfection (proteins or nucleic acid vectors), infection (viral vectors) or transduction (viral vectors) and may be 30 useful for complementation of mentioned wild type, attenuated, replication-defective or chimeric viruses.

... HETEROLOGOUS GENE SEQUENCES TO BE INSERTED

The present invention encompass engineering recombinant bovine or human parainfluenza viruses to express one or more heterologous sequences, wherein the 5 heterologous sequences encode gene products or fragments of gene products that are preferably antigenic and/or immunogenic. As used herein, the term "antigenic" refers to the ability of a molecule to bind antibody or MHC molecules. The term "immunogenic" refers to the ability of a molecule to generate immune response in a host.

In a preferred embodiment, the heterologous nucleotide sequence to be inserted is 10 derived from a negative strand RNA virus, including but not limited to, influenza virus, parainfluenza virus, respiratory syncytial virus, mammalian metapneumovirus (*e.g.*, human metapneumovirus) and avian pneumovirus. In a preferred embodiment, the heterologous sequence to be inserted includes, but is not limited to, a sequence that encodes a F or HN gene of human PIV, a F gene of RSV, a HA gene of influenza virus type A, B, or C, a F gene 15 of human MPV, a F gene of avian pneumovirus, or an immunogenic and/or antigenic fragment thereof.

In some embodiments, the heterologous nucleotide sequence to be inserted is derived from a human metapneumovirus and/or an avian pneumovirus. In certain embodiments, the heterologous nucleotide sequence to be inserted is derived from (a) a human 20 metapneumovirus and a respiratory syncytial virus; and/or (b) an avian pneumovirus and a respiratory syncytial virus.

In certain preferred embodiments of the invention, the heterologous nucleotide sequence to be inserted is derived from a F gene from a human metapneumovirus and/or an avian pneumovirus. In certain embodiments, the F gene is derived from (a) a human 25 metapneumovirus and a respiratory syncytial virus; and/or (b) an avian pneumovirus and a respiratory syncytial virus.

In certain embodiments of the invention, the heterologous nucleotide sequence to be inserted is a G gene derived from a human metapneumovirus and/or an avian pneumovirus.

In certain embodiments, the G gene is derived from (a) a human metapneumovirus and a 30 respiratory syncytial virus; and/or (b) an avian pneumovirus and a respiratory syncytial virus.

In certain embodiments, any combination of different F genes and/or different G genes derived from human metapneumovirus, avian pneumovirus, and respiratory syncytial virus can be inserted into the virus of the invention with the proviso that in all embodiments

5 at least one heterologous sequence derived from either human metapneumovirus or avian pneumovirus is present in the recombinant parainfluenza virus of the invention.

In certain embodiments, the nucleotide sequence to be inserted is a nucleotide sequence encoding a F protein derived from a human metapneumovirus. In certain other embodiments, the nucleotide sequence to be inserted is a nucleotide sequence encoding a G 10 protein derived from a human metapneumovirus. In yet other embodiments, the nucleotide sequence to be inserted is a nucleotide sequence encoding a F protein derived from an avian pneumovirus. In yet other embodiments, the nucleotide sequence to be inserted is a nucleotide sequence encoding a G protein derived from an avian pneumovirus. With the proviso that in all embodiments of the invention at least one heterologous nucleotide 15 sequence is derived from a metapneumovirus, the heterologous nucleotide sequence to be inserted encodes a F protein or a G protein of a respiratory syncytial virus.

In certain embodiments, the nucleotide sequence to be inserted encodes a chimeric F protein or a chimeric G protein. A chimeric F protein comprises parts of F proteins from different viruses, such as a human metapneumovirus, avian pneumovirus and/or respiratory 20 syncytial virus. A chimeric G protein comprises parts of G proteins from different viruses, such as a human metapneumovirus, avian pneumovirus and/or respiratory syncytial virus. In a specific embodiment, the F protein comprises an ectodomain of a F protein of a metapneumovirus, a transmembrane domain of a F protein of a parainfluenza virus, and 25 luminal domain of a F protein of a parainfluenza virus. In certain embodiments, the nucleic acid to be inserted encodes a F protein, wherein the transmembrane domain of the F protein is deleted so that a soluble F protein is expressed.

In certain specific embodiments, the heterologous nucleotide sequence of the invention is any one of SEQ ID NO:1 through SEQ ID NO:5, SEQ ID NO:14, and SEQ ID NO:15 (see Table 16). In certain specific embodiments, the nucleotide sequence encodes a 30 protein of any one of SEQ ID NO:6 through SEQ ID NO:13, SEQ ID NO:16, and SEQ ID

NO:17 (see Table 16). In certain specific embodiments, the nucleotide sequence encodes a protein of any one of SEQ ID NO. 314 to 389.

For heterologous nucleotide sequences derived from respiratory syncytial virus see,
5 e.g., PCT/US98/20230, which is hereby incorporated by reference in its entirety.

In a preferred embodiment, heterologous gene sequences that can be expressed into the chimeric viruses of the invention include but are not limited to those encoding antigenic epitopes and glycoproteins of viruses, such as influenza glycoproteins, in particular hemagglutinin H5, H7, respiratory syncytial virus epitopes, New Castle Disease virus
10 epitopes, Sendai virus and infectious Laryngotracheitis virus (ILV), that result in respiratory disease. In a most preferred embodiment, the heterologous nucleotide sequences are derived from a metapneumovirus, such as human metapneumovirus and/or avian pneumovirus. In yet another embodiment of the invention, heterologous gene sequences that can be engineered into the chimeric viruses of the invention include, but are not limited to, those
15 encoding viral epitopes and glycoproteins of viruses, such as hepatitis B virus surface antigen, hepatitis A or C virus surface glycoproteins of Epstein Barr virus, glycoproteins of human papilloma virus, simian virus 5 or mumps virus, West Nile virus, Dengue virus, glycoproteins of herpesviruses, VPI of poliovirus, and sequences derived from a human immunodeficiency virus (HIV), preferably type 1 or type 2. In yet another embodiment,
20 heterologous gene sequences that can be engineered into chimeric viruses of the invention include, but are not limited to, those encoding Marek's Disease virus (MDV) epitopes, epitopes of infectious Bursal Disease virus (IBDV), epitopes of Chicken Anemia virus, infectious laryngotracheitis virus (ILV), Avian Influenza virus (AIV), rabies, feline leukemia virus, canine distemper virus, vesicular stomatitis virus, and swinepox virus (*see Fields et al.*
25 (ed.), 1991, FUNDAMENTAL VIROLOGY, Second Edition, Raven Press, New York, incorporated by reference herein in its entirety).

Other heterologous sequences of the present invention include those encoding antigens that are characteristic of autoimmune diseases. These antigens will typically be derived from the cell surface, cytoplasm, nucleus, mitochondria and the like of mammalian
30 tissues, including antigens characteristic of diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, pernicious anemia, Addison's disease,

scleroderma, autoimmune atrophic gastritis, juvenile diabetes, and discold lupus erythematosus.

- Antigens that are allergens generally include proteins or glycoproteins, including
- 5 antigens derived from pollens, dust, molds, spores, dander, insects and foods. In addition, antigens that are characteristic of tumor antigens typically will be derived from the cell surface, cytoplasm, nucleus, organelles and the like of cells of tumor tissue. Examples include antigens characteristic of tumor proteins, including proteins encoded by mutated oncogenes; viral proteins associated with tumors; and glycoproteins. Tumors include, but are
- 10 not limited to, those derived from the types of cancer: lip, nasopharynx, pharynx and oral cavity, esophagus, stomach, colon, rectum, liver, gall bladder, pancreas, larynx, lung and bronchus, melanoma of skin, breast, cervix, uterine, ovary, bladder, kidney, uterus, brain and other parts of the nervous system, thyroid, prostate, testes, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma and leukemia.

- 15 In one specific embodiment of the invention, the heterologous sequences are derived from the genome of human immunodeficiency virus (HIV), preferably human immunodeficiency virus-1 or human immunodeficiency virus-2. In another embodiment of the invention, the heterologous coding sequences may be inserted within a PIV gene coding sequence such that a chimeric gene product, that contains the heterologous peptide sequence
- 20 within the PIV viral protein, is expressed. In such an embodiment of the invention, the heterologous sequences may also be derived from the genome of a human immunodeficiency virus, preferably of human immunodeficiency virus-1 or human immunodeficiency virus-2.

- In instances whereby the heterologous sequences are HIV-derived, such sequences may include, but are not limited to sequences derived from the env gene (*i.e.*, sequences
- 25 encoding all or part of gp160, gp120, and/or gp41), the pol gene (*i.e.*, sequences encoding all or part of reverse transcriptase, endonuclease, protease, and/or integrase), the gag gene (*i.e.*, sequences encoding all or part of p7, p6, p55, p17/18, p24/25) tat, rev, nef, vif, vpu, vpr, and/or vpx.

- In another embodiment, heterologous gene sequences that can be engineered into the
- 30 chimeric viruses include those that encode proteins with immunopotentiating activities. Examples of immunopotentiating proteins include, but are not limited to, cytokines,

interferon type 1, gamma interferon, colony stimulating factors, and interleukin -1, -2, -4, -5, -6, -12.

In addition, other heterologous gene sequences that may be engineered into the
5 chimeric viruses include those encoding antigens derived from bacteria such as bacterial surface glycoproteins, antigens derived from fungi, and antigens derived from a variety of other pathogens and parasites. Examples of heterologous gene sequences derived from bacterial pathogens include, but are not limited to, those encoding antigens derived from species of the following genera: *Salmonella*, *Shigella*, *Chlamydia*, *Helicobacter*, *Yersinia*,
10 *Bordatella*, *Pseudomonas*, *Neisseria*, *Vibrio*, *Haemophilus*, *Mycoplasma*, *Streptomyces*, *Treponema*, *Coxiella*, *Ehrlichia*, *Brucella*, *Streptobacillus*, *Fusospirocheta*, *Spirillum*, *Ureaplasma*, *Spirochaeta*, *Mycoplasma*, *Actinomycetes*, *Borrelia*, *Bacteroides*, *Trichomorpha*, *Branhamella*, *Pasteurella*, *Clostridium*, *Corynebacterium*, *Listeria*, *Bacillus*, *Erysipelothrix*, *Rhodococcus*, *Escherichia*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, *Serratia*,
15 *Staphylococcus*, *Streptococcus*, *Legionella*, *Mycobacterium*, *Proteus*, *Campylobacter*, *Enterococcus*, *Acinetobacter*, *Morganella*, *Moraxella*, *Citrobacter*, *Rickettsia*, *Rochlimeae*, as well as bacterial species such as: *P. aeruginosa*; *E. coli*, *P. cepacia*, *S. epidermidis*, *E. faecalis*, *S. pneumoniae*, *S. aureus*, *N. meningitidis*, *S. pyogenes*, *Pasteurella multocida*, *Treponema pallidum*, and *P. mirabilis*.

20 Examples of heterologous gene sequences derived from pathogenic fungi, include, but are not limited to, those encoding antigens derived from fungi such as *Cryptococcus neoformans*; *Blastomyces dermatitidis*; *Aiellomyces dermatitidis*; *Histoplasma capsulatum*; *Coccidioides immitis*; *Candida species*, including *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. guilliermondii* and *C. krusei*, *Aspergillus species*, including *A. fumigatus*, *A. flavus* and *A. niger*, *Rhizopus species*; *Rhizomucor species*; *Cunninghamella species*; *Apophysomyces species*, including *A. saksenaea*, *A. mucor* and *A. absidia*; *Sporothrix schenckii*, *Paracoccidioides brasiliensis*; *Pseudallescheria boydii*, *Torulopsis glabrata*; *Trichophyton species*, *Microsporum species* and *Dermatophytes species*, as well as any other yeast or fungus now known or later identified to be pathogenic.

25 Finally, examples of heterologous gene sequences derived from parasites include, but are not limited to, those encoding antigens derived from members of the Apicomplexa

phylum such as, for example, *Babesia*, *Toxoplasma*, *Plasmodium*, *Eimeria*, *Isospora*, *Atoxoplasma*, *Cystoisospora*, *Hammondia*, *Besniotia*, *Sarcocystis*, *Frenkelia*, *Haemoproteus*, *Leucocytozoon*, *Theileria*, *Perkinsus* and *Gregarina* spp.; *Pneumocystis carinii*; members of
5 the Microspora phylum such as, for example, *Nosema*, *Enterocytozoon*, *Encephalitozoon*, *Septata*, *Mrazekia*, *Amblyospora*, *Ameson*, *Glugea*, *Pleistophora* and *Microsporidium* spp.; and members of the Ascetospora phylum such as, for example, *Haplosporidium* spp., as well as species including *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malaria*; *Toxoplasma gondii*; *Leishmania mexicana*, *L. tropica*, *L. major*, *L. aethiopica*, *L. donovani*, *Trypanosoma cruzi*, *T. brucei*, *Schistosoma mansoni*; *S. haematobium*, *S. japonium*; *Trichinella spiralis*; *Wuchereria bancrofti*; *Brugia malayli*; *Entamoeba histolytica*; *Enterobius vermicularis*; *Taenia solium*, *T. saginata*, *Trichomonas vaginalis*, *T. hominis*, *T. tenax*; *Giardia lamblia*; *Cryptosporidium parvum*; *Pneumocytis carinii*, *Babesia bovis*, *B. divergens*, *B. microti*, *Isospora belli*, *L. hominis*; *Dientamoeba fragilis*; *Onchocerca volvulus*; *Ascaris lumbricoides*; *Necator americanus*; *Ancylostoma duodenale*; *Strongyloides stercoralis*; *Capillaria philippinensis*; *Angiostrongylus cantonensis*; *Hymenolepis nana*; *Diphyllobothrium latum*; *Echinococcus granulosus*, *E. multilocularis*; *Paragonimus westermani*, *P. caliensis*; *Chlonorchis sinensis*; *Opisthorchis felineas*, *G. Viverini*, *Fasciola hepatica*, *Sarcoptes scabiei*, *Pediculus humanus*; *Phthirus pubis*; and *Dermatobia hominis*,
10 as well as any other parasite now known or later identified to be pathogenic.
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5.1.2. METAPNEUMOVIRAL SEQUENCES TO BE INSERTED

proteins of a mammalian MPV. The invention further relates to nucleic acid sequences encoding fusion proteins, wherein the fusion protein contains a protein of a
25 mammalian MPV or a fragment thereof and one or more peptides or proteins that are not derived from mammalian MPV. In a specific embodiment, a fusion protein of the invention contains a protein of a mammalian MPV or a fragment thereof and a peptide tag, such as, but not limited to a polyhistidine tag. The invention further relates to fusion proteins, wherein the fusion protein contains a protein of a mammalian MPV or a fragment thereof and one or
30 more peptides or proteins that are not derived from mammalian MPV. The invention also relates to derivatives of nucleic acids encoding a protein of a mammalian MPV. The

invention also relates to derivatives of proteins of a mammalian MPV. A derivative can be, but is not limited to, mutant forms of the protein, such as, but not limited to, additions, deletions, truncations, substitutions, and inversions. A derivative can further be a chimeric 5 form of the protein of the mammalian MPV, wherein at least one domain of the protein is derived from a different protein. A derivative can also be a form of a protein of a mammalian MPV that is covalently or non-covalently linked to another molecule, such as, e.g., a drug.

The viral isolate termed NL/1/00 (also 00-1) is a mammalian MPV of variant A1 and 10 its genomic sequence is shown in SEQ ID NO:95. The viral isolate termed NL/17/00 is a mammalian MPV of variant A2 and its genomic sequence is shown in SEQ ID NO:96. The viral isolate termed NL/1/99 (also 99-1) is a mammalian MPV of variant B1 and its genomic sequence is shown in SEQ ID NO:94. The viral isolate termed NL/1/94 is a mammalian 15 MPV of variant B2 and its genomic sequence is shown in SEQ ID NO:97. A list of sequences disclosed in the present application and the corresponding SEQ ID Nos is set forth in Table 16.

The protein of a mammalian MPV can be a N protein, a P protein, a M protein, a F protein, a M2-1 protein or a M2-2 protein or a fragment thereof. A fragment of a protein of a mammalian MPV can be can be at least 25 amino acids, at least 50 amino acids, at least 75 20 amino acids, at least 100 amino acids, at least 125 amino acids, at least 150 amino acids, at least 175 amino acids, at least 200 amino acids, at least 225 amino acids, at least 250 amino acids, at least 275 amino acids, at least 300 amino acids, at least 325 amino acids, at least 350 amino acids, at least 375 amino acids, at least 400 amino acids, at least 425 amino acids, at least 450 amino acids, at least 475 amino acids, at least 500 amino acids, at least 750 amino 25 acids, at least 1000 amino acids, at least 1250 amino acids, at least 1500 amino acids, at least 1750 amino acids, at least 2000 amino acids or at least 2250 amino acids in length. A fragment of a protein of a mammalian MPV can be can be at most 25 amino acids, at most 50 amino acids, at most 75 amino acids, at most 100 amino acids, at most 125 amino acids, at most 150 amino acids, at most 175 amino acids, at most 200 amino acids, at most 225 amino 30 acids, at most 250 amino acids, at most 275 amino acids, at most 300 amino acids, at most 325 amino acids, at most 350 amino acids, at most 375 amino acids, at most 400 amino

acids, at most 425 amino acids, at most 450 amino acids, at most 475 amino acids, at most 500 amino acids, at most 750 amino acids, at most 1000 amino acids, at most 1250 amino acids, at most 1500 amino acids, at most 1750 amino acids, at most 2000 amino acids or at 5 most 2250 amino acids in length.

In certain embodiments of the invention, the protein of a mammalian MPV is a N protein, wherein the N protein is phylogenetically closer related to a N protein of a mammalian MPV, such as the N protein encoded by, e.g., the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97, (see also Table 16 for a 10 description of the SEQ ID Nos) than it is related to the N protein of APV type C. In certain embodiments of the invention, the protein of a mammalian MPV is a P protein, wherein the P protein is phylogenetically closer related to a P protein of a mammalian MPV, such as the P protein encoded by, e.g., the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97, than it is related to the N protein of APV type C. In certain 15 embodiments of the invention, the protein of a mammalian MPV is a M protein, wherein the M protein is closer related to a M protein of a mammalian MPV, such as the M protein encoded by, e.g., the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97, than it is related to the M protein of APV type C. In certain embodiments of the invention, the protein of a mammalian MPV is a F protein, wherein the F protein is 20 phylogenetically closer related to a F protein of a mammalian MPV, such as the F protein encoded by, e.g., the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97, than it is related to the F protein of APV type C. In certain embodiments of the invention, the protein of a mammalian MPV is a M2-1 protein, wherein the M2-1 protein is phylogenetically closer related to a M2-1 protein of a mammalian MPV, such as the M2-1 25 protein encoded by, e.g., the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97, than it is related to the M2-1 protein of APV type C. In certain embodiments of the invention, the protein of a mammalian MPV is a M2-2 protein, wherein the M2-2 protein is phylogenetically closer related to a M2-2 protein of a mammalian MPV, such as the M2-2 protein encoded by, e.g., the viral genome of SEQ ID NO:94, SEQ ID 30 NO:95, SEQ ID NO:96, or SEQ ID NO:97, than it is related to the M2-2 protein of APV type C. In certain embodiments of the invention, the protein of a mammalian MPV is a G protein,

wherein the G protein is phylogenetically closer related to a G protein of a mammalian MPV, such as the G protein encoded by, e.g., the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97, than it is related to any protein of APV type C. In certain 5 embodiments of the invention, the protein of a mammalian MPV is a SH protein, wherein the SH protein is phylogenetically closer related to a SH protein of a mammalian MPV, such as the SH protein encoded by, e.g., the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97, than it is related to any protein of APV type C. In certain 10 embodiments of the invention, the protein of a mammalian MPV is a L protein, wherein the L protein is phylogenetically closer related to a L protein of a mammalian MPV, such as the SH protein encoded by, e.g., the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97, than it is related to any protein of APV type C.

In certain embodiments of the invention, the protein of a mammalian MPV is a N protein, wherein the N protein is at least 60%, at least 65%, at least 70%, at least 75%, at 15 least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to the amino acid sequence of a N protein encoded by the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97 (the amino acid sequences of the respective N proteins are disclosed in SEQ ID NO:366-369; see also Table 16). In certain embodiments of the invention, the protein of a mammalian MPV is a N 20 protein, wherein the P protein is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to the amino acid sequence of a P protein encoded by the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97 (the amino acid sequences of the respective P proteins are disclosed in SEQ ID NO:78-85; see also Table 16). In certain 25 embodiments of the invention, the protein of a mammalian MPV is a M protein, wherein the M protein is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to the amino acid sequence of a M protein encoded by the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97 (the amino acid sequences of the respective M 30 proteins are disclosed in SEQ ID NO:358-361; see also Table 16). In certain embodiments of the invention, the protein of a mammalian MPV is a F protein, wherein the F protein is at

least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to the amino acid sequence of a F protein encoded by the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97 (the amino acid sequences of the respective F proteins are disclosed in SEQ ID NO:18-25; see also Table 16). In certain embodiments of the invention, the protein of a mammalian MPV is a M2-1 protein, wherein the M2-1 protein is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to the amino acid sequence of a M2-1 protein encoded by the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97 (the amino acid sequences of the respective M2-1 proteins are disclosed in SEQ ID NO:42-49; see also Table 16). In certain embodiments of the invention, the protein of a mammalian MPV is a M2-2 protein, wherein the M2-2 protein is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to the amino acid sequence of a M2-2 protein encoded by the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97 (the amino acid sequences of the respective M2-2 proteins are disclosed in SEQ ID NO:50-57; see also Table 16). In certain embodiments of the invention, the protein of a mammalian MPV is a G protein, wherein the G protein is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to the amino acid sequence of a G protein encoded by the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97 (the amino acid sequences of the respective G proteins are disclosed in SEQ ID NO:26-33; see also Table 16). In certain embodiments of the invention, the protein of a mammalian MPV is a SH protein, wherein the SH protein is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to the amino acid sequence of a SH protein encoded by the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97 (the amino acid sequences of the respective SH proteins are disclosed in SEQ ID NO:86-93; see also Table 16). In certain embodiments of the invention, the protein of a mammalian MPV is a L protein, wherein the L protein is at least 60%, at least 65%, at least 70%, at least 75%, at

least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to the amino acid sequence of a L protein encoded by the viral genome of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97 (the amino acid sequences of the respective L proteins are disclosed in SEQ ID NO:34-41; see also Table 16).

A fragment of a protein of mammalian MPV is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to the homologous protein encoded by the virus of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97 over the portion of the protein 10 that is homologous to the fragment. In a specific, illustrative embodiment, the invention provides a fragment of the F protein of a mammalian MPV that contains the ectodomain of the F protein and homologs thereof. The homolog of the fragment of the F protein that contains the ectodomain is at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% 15 identical to the corresponding fragment containing the ectodomain of the F protein encoded by a virus of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97 (the amino acid sequences of the respective F proteins are disclosed in SEQ ID NO:18-25; see also Table 16).

In certain embodiments, the invention provides a protein of a mammalian MPV of 20 subgroup A and fragments thereof. The invention provides a N protein of a mammalian MPV of subgroup A, wherein the N protein is phylogenetically closer related to the N protein encoded by a virus of SEQ ID NO:95 or SEQ ID NO:96 than it is related to the N protein encoded by a virus encoded by SEQ ID NO:94 or SEQ ID NO:97. The invention provides a G protein of a mammalian MPV of subgroup A, wherein the G protein is phylogenetically 25 closer related to the G protein encoded by a virus of SEQ ID NO:95 or SEQ ID NO:96 than it is related to the G protein encoded by a virus encoded by SEQ ID NO:94 or SEQ ID NO:97. The invention provides a P protein of a mammalian MPV of subgroup A, wherein the P protein is phylogenetically closer related to the P protein encoded by a virus of SEQ ID NO:95 or SEQ ID NO:96 than it is related to the P protein encoded by a virus encoded by 30 SEQ ID NO:94 or SEQ ID NO:97. The invention provides a M protein of a mammalian MPV of subgroup A, wherein the M protein is phylogenetically closer related to the M

protein encoded by a virus of SEQ ID NO:95 or SEQ ID NO:96 than it is related to the M protein encoded by a virus encoded by SEQ ID NO:94 or SEQ ID NO:97. The invention provides a N protein of a mammalian MPV of subgroup A, wherein the F protein is

5 phylogenetically closer related to the F protein encoded by a virus of SEQ ID NO:95 or SEQ ID NO:96 than it is related to the F protein encoded by a virus encoded by SEQ ID NO:94 or SEQ ID NO:97. The invention provides a M2-1 protein of a mammalian MPV of subgroup A, wherein the M2-1 protein is phylogenetically closer related to the M2-1 protein encoded by a virus of SEQ ID NO:95 or SEQ ID NO:96 than it is related to the M2-1 protein encoded

10 by a virus encoded by SEQ ID NO:94 or SEQ ID NO:97. The invention provides a M2-2 protein of a mammalian MPV of subgroup A, wherein the M2-2 protein is phylogenetically closer related to the M2-2 protein encoded by a virus of SEQ ID NO:95 or SEQ ID NO:96 than it is related to the M2-2 protein encoded by a virus encoded by SEQ ID NO:94 or SEQ ID NO:97. The invention provides a SH protein of a mammalian MPV of subgroup A,

15 wherein the SH protein is phylogenetically closer related to the SH protein encoded by a virus of SEQ ID NO:95 or SEQ ID NO:96 than it is related to the SH protein encoded by a virus encoded by SEQ ID NO:94 or SEQ ID NO:97. The invention provides a L protein of a mammalian MPV of subgroup A, wherein the L protein is phylogenetically closer related to the L protein encoded by a virus of SEQ ID NO:95 or SEQ ID NO:96 than it is related to the

20 L protein encoded by a virus encoded by SEQ ID NO:94 or SEQ ID NO:97.

In other embodiments, the invention provides a protein of a mammalian MPV of subgroup B or fragments thereof. The invention provides a N protein of a mammalian MPV of subgroup B, wherein the N protein is phylogenetically closer related to the N protein encoded by a virus of SEQ ID NO:94 or SEQ ID NO:97 than it is related to the N protein encoded by a virus encoded by SEQ ID NO:95 or SEQ ID NO:96. The invention provides a G protein of a mammalian MPV of subgroup A, wherein the G protein is phylogenetically closer related to the G protein encoded by a virus of SEQ ID NO:94 or SEQ ID NO:97 than it is related to the G protein encoded by a virus encoded by SEQ ID NO:95 or SEQ ID NO:96.

25 The invention provides a P protein of a mammalian MPV of subgroup A, wherein the P protein is phylogenetically closer related to the P protein encoded by a virus of SEQ ID NO:94 or SEQ ID NO:97 than it is related to the P protein encoded by a virus encoded by

SEQ ID NO:95 or SEQ ID NO:96. The invention provides a M protein of a mammalian MPV of subgroup A, wherein the M protein is phylogenetically closer related to the M protein encoded by a virus of SEQ ID NO:94 or SEQ ID NO:97 than it is related to the M 5 protein encoded by a virus encoded by SEQ ID NO:95 or SEQ ID NO:96. The invention provides a N protein of a mammalian MPV of subgroup A, wherein the F protein is phylogenetically closer related to the F protein encoded by a virus of SEQ ID NO:94 or SEQ ID NO:97 than it is related to the F protein encoded by a virus encoded by SEQ ID NO:95 or SEQ ID NO:96. The invention provides a M2-1 protein of a mammalian MPV of subgroup 10 A, wherein the M2-1 protein is phylogenetically closer related to the M2-1 protein encoded by a virus of SEQ ID NO:94 or SEQ ID NO:97 than it is related to the M2-1 protein encoded by a virus encoded by SEQ ID NO:95 or SEQ ID NO:96. The invention provides a M2-2 protein of a mammalian MPV of subgroup A, wherein the M2-2 protein is phylogenetically closer related to the M2-2 protein encoded by a virus of SEQ ID NO:94 or SEQ ID NO:97 than it is related to the M2-2 protein encoded by a virus encoded by SEQ ID NO:95 or SEQ ID NO:96. The invention provides a SH protein of a mammalian MPV of subgroup A, 15 wherein the SH protein is phylogenetically closer related to the SH protein encoded by a virus of SEQ ID NO:94 or SEQ ID NO:97 than it is related to the SH protein encoded by a virus encoded by SEQ ID NO:95 or SEQ ID NO:96. The invention provides a L protein of a mammalian MPV of subgroup A, wherein the L protein is phylogenetically closer related to the L protein encoded by a virus of SEQ ID NO:94 or SEQ ID NO:97 than it is related to the L protein encoded by a virus encoded by SEQ ID NO:95 or SEQ ID NO:96. 20

The invention provides a G protein of a mammalian MPV variant B1, wherein the G protein of a mammalian MPV variant B1 is phylogenetically closer related to the G protein of the prototype of variant B1, isolate NL/1/99, than it is related to the G protein of the prototype of variant A1, isolate NL/1/00, the G protein of the prototype of A2, isolate NL/17/00, or the G protein of the prototype of B2, isolate NL/1/94. The invention provides a G protein of a mammalian MPV variant B1, wherein the amino acid sequence of the G protein is at least 66%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at 25 30 least 95%, at least 98%, or at least 99% or at least 99.5% identical to the G protein of a mammalian MPV variant B1 as represented by the prototype NL/1/99 (SEQ ID NO:28). In a

specific embodiment, the G protein of a mammalian MPV has the amino acid sequence of SEQ ID NO:119-153. The invention provides a N protein of a mammalian MPV variant B1, wherein the N protein of a mammalian MPV variant B1 is phylogenetically closer related to the N protein of the prototype of variant B1, isolate NL/1/99, than it is related to the N protein of the prototype of variant A1, isolate NL/1/00, the N protein of the prototype of A2, isolate NL/17/00, or the N protein of the prototype of B2, isolate NL/1/94. The invention provides a N protein of a mammalian MPV variant B1, wherein the amino acid sequence of the N protein is at least 98.5% or at least 99% or at least 99.5% identical to the N protein of a mammalian MPV variant B1 as represented by the prototype NL/1/99 (SEQ ID NO:72).

The invention provides a P protein of a mammalian MPV variant B1, wherein the P protein of a mammalian MPV variant B1 is phylogenetically closer related to the P protein of the prototype of variant B1, isolate NL/1/99, than it is related to the P protein of the prototype of variant A1, isolate NL/1/00, the P protein of the prototype of A2, isolate NL/17/00, or the P protein of the prototype of B2, isolate NL/1/94. The invention provides a P protein of a mammalian MPV variant B1, wherein the amino acid sequence of the P protein is at least 96%, at least 98%, or at least 99% or at least 99.5% identical to the P protein of a mammalian MPV variant B1 as represented by the prototype NL/1/99 (SEQ ID NO:80). The invention provides a M protein of a mammalian MPV variant B1, wherein the M protein of a mammalian MPV variant B1 is phylogenetically closer related to the M protein of the prototype of variant B1, isolate NL/1/99, than it is related to the M protein of the prototype of variant A1, isolate NL/1/00, the M protein of the prototype of A2, isolate NL/17/00, or the M protein of the prototype of B2, isolate NL/1/94. The invention provides a M protein of a mammalian MPV variant B1, wherein the amino acid sequence of the M protein is identical to the M protein of a mammalian MPV variant B1 as represented by the prototype NL/1/99 (SEQ ID NO:64). The invention provides a F protein of a mammalian MPV variant B1, wherein the F protein of a mammalian MPV variant B1 is phylogenetically closer related to the F protein of variant B1, isolate NL/1/99, than it is related to the F protein of variant A1, isolate NL/1/00, the F protein of prototype A2, isolate NL/17/00, or the F protein of the prototype of B2, isolate NL/1/94. The invention provides a F protein of mammalian MPV variant B1, wherein the amino acid sequence of the F protein is identical at least 99%

identical, to the F protein of a mammalian MPV variant B1 as represented by the prototype NL/1/99 (SEQ ID NO:20). In a specific embodiment, the F protein of a mammalian MPV has the amino acid sequence of SEQ ID NO: 248-327. The invention provides a M2-1

5 protein of a mammalian MPV variant B1, wherein the M2-1 protein of a mammalian MPV variant B1 is phylogenetically closer related to the M2-1 protein of the prototype of variant B1, isolate NL/1/99, than it is related to the M2-1 protein of the prototype of variant A1, isolate NL/1/00, the M2-1 protein of the prototype of A2, isolate NL/17/00, or the M2-1 protein of the prototype of B2, isolate NL/1/94. The invention provides a M2-1 protein of a

10 mammalian MPV variant B1, wherein the amino acid sequence of the M2-1 protein is at least 98% or at least 99% or at least 99.5% identical the M2-1 protein of a mammalian MPV variant B1 as represented by the prototype NL/1/99 (SEQ ID NO:44). The invention provides a M2-2 protein of a mammalian MPV variant B1, wherein the M2-2 protein of a mammalian MPV variant B1 is phylogenetically closer related to the M2-2 protein of the

15 prototype of variant B1, isolate NL/1/99, than it is related to the M2-2 protein of the prototype of variant A1, isolate NL/1/00, the M2-2 protein of the prototype of A2, isolate NL/17/00, or the M2-2 protein of the prototype of B2, isolate NL/1/94. The invention provides a M2-2 protein of a mammalian MPV variant B1, wherein the amino acid sequence of the M2-2 protein is at least 99%or at least 99.5% identical the M2-2 protein of a

20 mammalian MPV variant B1 as represented by the prototype NL/1/99 (SEQ ID NO:52). The invention provides a SH protein of a mammalian MPV variant B1, wherein the SH protein of a mammalian MPV variant B1 is phylogenetically closer related to the SH protein of the prototype of variant B1, isolate NL/1/99, than it is related to the SH protein of the prototype of variant A1, isolate NL/1/00, the SH protein of the prototype of A2, isolate NL/17/00, or

25 the SH protein of the prototype of B2, isolate NL/1/94. The invention provides a SH protein of a mammalian MPV variant B1, wherein the amino acid sequence of the SH protein is at least 83%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% or at least 99.5% identical the SH protein of a mammalian MPV variant B1 as represented by the prototype NL/1/99 (SEQ ID NO:88). The invention provides a L protein of a mammalian

30 MPV variant B1, wherein the L protein of a mammalian MPV variant B1 is phylogenetically closer related to the L protein of the prototype of variant B1, isolate NL/1/99, than it is

related to the L protein of the prototype of variant A1, isolate NL/1/00, the L protein of the prototype of A2, isolate NL/17/00, or the L protein of the prototype of B2, isolate NL/1/94. The invention provides a L protein of a mammalian MPV variant B1, wherein the amino acid sequence of the L protein is at least 99% or at least 99.5% identical the L protein a mammalian MPV variant B1 as represented by the prototype NL/1/99 (SEQ ID NO:36).

The invention provides a G protein of a mammalian MPV variant A1, wherein the G protein of a mammalian MPV variant A1 is phylogenetically closer related to the G protein of the prototype of variant A1, isolate NL/1/00, than it is related to the G protein of the prototype of variant B1, isolate NL/1/99, the G protein of the prototype of A2, isolate NL/17/00, or the G protein of the prototype of B2, isolate NL/1/94. The invention provides a G protein of a mammalian MPV variant A1, wherein the amino acid sequence of the G protein is at least 66%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% or at least 99.5% identical to the G protein of a mammalian MPV variant A1 as represented by the prototype NL/1/00 (SEQ ID NO:26). The invention provides a N protein of a mammalian MPV variant A1, wherein the N protein of a mammalian MPV variant A1 is phylogenetically closer related to the N protein of the prototype of variant A1, isolate NL/1/00, than it is related to the N protein of the prototype of variant B1, isolate NL/1/99, the N protein of the prototype of A2, isolate NL/17/00, or the N protein of the prototype of B2, isolate NL/1/94. The invention provides a N protein of a mammalian MPV variant A1, wherein the amino acid sequence of the N protein is at least 99.5% identical to the N protein of a mammalian MPV variant A1 as represented by the prototype NL/1/00 (SEQ ID NO:70). The invention provides a P protein of a mammalian MPV variant A1, wherein the P protein of a mammalian MPV variant A1 is phylogenetically closer related to the P protein of the prototype of variant A1, isolate NL/1/00, than it is related to the P protein of the prototype of variant B1, isolate NL/1/99, the P protein of the prototype of A2, isolate NL/17/00, or the P protein of the prototype of B2, isolate NL/1/94. The invention provides a P protein of a mammalian MPV variant A1, wherein the amino acid sequence of the P protein is at least 96%, at least 98%, or at least 99% or at least 99.5% identical to the P protein of a mammalian MPV variant A1 as represented by the prototype NL/1/00 (SEQ ID NO:78). The invention provides a M protein of a mammalian MPV

variant A1, wherein the M protein of a mammalian MPV variant A1 is phylogenetically closer related to the M protein of the prototype of variant A1, isolate NL/1/00, than it is related to the M protein of the prototype of variant B1, isolate NL/1/99, the M protein of the prototype of A2, isolate NL/17/00, or the M protein of the prototype of B2, isolate NL/1/94.

5 The invention provides a M protein of a mammalian MPV variant A1, wherein the amino acid sequence of the M protein is at least 99% or at least 99.5% identical to the M protein of a mammalian MPV variant A1 as represented by the prototype NL/1/00 (SEQ ID NO:62).

The invention provides a F protein of a mammalian MPV variant A1, wherein the F protein

10 of a mammalian MPV variant A1 is phylogenetically closer related to the F protein of the prototype of variant A1, isolate NL/1/00, than it is related to the F protein of the prototype of variant B1, isolate NL/1/99, the F protein of the prototype of A2, isolate NL/17/00, or the F protein of the prototype of B2, isolate NL/1/94. The invention provides a F protein of a mammalian MPV variant A1, wherein the amino acid sequence of the F protein is at least

15 98% or at least 99% or at least 99.5% identical to the F protein of a mammalian MPV variant A1 as represented by the prototype NL/1/00 (SEQ ID NO:18). The invention provides a M2-1 protein of a mammalian MPV variant A1, wherein the M2-1 protein of a mammalian MPV variant A1 is phylogenetically closer related to the M2-1 protein of the prototype of variant A1, isolate NL/1/00, than it is related to the M2-1 protein of the prototype of variant B1,

20 isolate NL/1/99, the M2-1 protein of the prototype of A2, isolate NL/17/00, or the M2-1 protein of the prototype of B2, isolate NL/1/94. The invention provides a M2-1 protein of a mammalian MPV variant A1, wherein the amino acid sequence of the M2-1 protein is at least 99% or at least 99.5% identical to the M2-1 protein of a mammalian MPV variant A1 as represented by the prototype NL/1/00 (SEQ ID NO:42). The invention provides a M2-2

25 protein of a mammalian MPV variant A1, wherein the M2-2 protein of a mammalian MPV variant A1 is phylogenetically closer related to the M2-2 protein of the prototype of variant A1, isolate NL/1/00, than it is related to the M2-2 protein of the prototype of variant B1, isolate NL/1/99, the M2-2 protein of the prototype of A2, isolate NL/17/00, or the M2-2 protein of the prototype of B2, isolate NL/1/94. The invention provides a M2-2 protein of a

30 mammalian MPV variant A1, wherein the amino acid sequence of the M2-2 protein is at least 96% or at least 99% or at least 99.5% identical to the M2-2 protein of a mammalian

MPV variant A1 as represented by the prototype NL/1/00 (SEQ ID NO:50). The invention provides a SH protein of a mammalian MPV variant A1, wherein the SH protein of a mammalian MPV variant A1 is phylogenetically closer related to the SH protein of the prototype of variant A1, isolate NL/1/00, than it is related to the SH protein of the prototype of variant B1, isolate NL/1/99, the SH protein of the prototype of A2, isolate NL/17/00, or the SH protein of the prototype of B2, isolate NL/1/94. The invention provides a SH protein of a mammalian MPV variant A1, wherein the amino acid sequence of the SH protein is at least 84%, at least 90%, at least 95%, at least 98%, or at least 99% or at least 99.5% identical to the SH protein of a mammalian MPV variant A1 as represented by the prototype NL/1/00 (SEQ ID NO:86). The invention provides a L protein of a mammalian MPV variant A1, wherein the L protein of a mammalian MPV variant A1 is phylogenetically closer related to the L protein of the prototype of variant A1, isolate NL/1/00, than it is related to the L protein of the prototype of variant B1, isolate NL/1/99, the L protein of the prototype of A2, isolate NL/17/00, or the L protein of the prototype of B2, isolate NL/1/94. The invention provides a L protein of a mammalian MPV variant A1, wherein the amino acid sequence of the L protein is at least 99% or at least 99.5% identical to the L protein of a virus of a mammalian MPV variant A1 as represented by the prototype NL/1/00 (SEQ ID NO:34).

The invention provides a G protein of a mammalian MPV variant A2, wherein the G protein of a mammalian MPV variant A2 is phylogenetically closer related to the G protein of the prototype of variant A2, isolate NL/17/00, than it is related to the G protein of the prototype of variant B1, isolate NL/1/99, the G protein of the prototype of A1, isolate NL/1/00, or the G protein of the prototype of B2, isolate NL/1/94. The invention provides a G protein of a mammalian MPV variant A2, wherein the amino acid sequence of the G protein is at least 66%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99% or at least 99.5% identical to the G protein of a mammalian MPV variant A2 as represented by the prototype NL/17/00 (SEQ ID NO:27).

The invention provides a N protein of a mammalian MPV variant A2, wherein the N protein of a mammalian MPV variant A2 is phylogenetically closer related to the N protein of the prototype of variant A2, isolate NL/17/00, than it is related to the N protein of the prototype of variant B1, isolate NL/1/99, the N protein of the prototype of A1, isolate NL/1/00, or the N

- protein of the prototype of B2, isolate NL/1/94. The invention provides a N protein of a mammalian MPV variant A2, wherein the amino acid sequence of the N protein at least 99.5% identical to the N protein of a mammalian MPV variant A2 as represented by the
- 5 prototype NL/17/00 (SEQ ID NO:71). The invention provides a P protein of a mammalian MPV variant A2, wherein the P protein of a mammalian MPV variant A2 is phylogenetically closer related to the P protein of the prototype of variant A2, isolate NL/17/00, than it is related to the P protein of the prototype of variant B1, isolate NL/1/99, the P protein of the prototype of A1, isolate NL/1/00, or the P protein of the prototype of B2, isolate NL/1/94.
- 10 The invention provides a P protein of a mammalian MPV variant A2, wherein the amino acid sequence of the P protein is at least 96%, at least 98%, at least 99% or at least 99.5% identical to the P protein of a mammalian MPV variant A2 as represented by the prototype NL/17/00 (SEQ ID NO:79). The invention provides a M protein of a mammalian MPV variant A2, wherein the M protein of a mammalian MPV variant A2 is phylogenetically closer related to the M protein of the prototype of variant A2, isolate NL/17/00, than it is related to the M protein of the prototype of variant B1, isolate NL/1/99, the M protein of the prototype of A1, isolate NL/1/00, or the M protein of the prototype of B2, isolate NL/1/94.
- 15 The invention provides a M protein of a mammalian MPV variant A2, wherein the the amino acid sequence of the M protein is at least 99%, or at least 99.5% identical to the M protein of a mammalian MPV variant A2 as represented by the prototype NL/17/00 (SEQ ID NO:63).
- The invention provides a F protein of a mammalian MPV variant A2, wherein the F protein of a mammalian MPV variant A2 is phylogenetically closer related to the F protein of the prototype of variant A2, isolate NL/17/00, than it is related to the F protein of the prototype of variant B1, isolate NL/1/99, the F protein of the prototype of A1, isolate NL/1/00, or the F
- 20 protein of the prototype of B2, isolate NL/1/94. The invention provides a F protein of a mammalian MPV variant A2, wherein the amino acid sequence of the F protein is at least 98%, at least 99% or at least 99.5% identical to the F protein of a mammalian MPV variant A2 as represented by the prototype NL/17/00 (SEQ ID NO:19). The invention provides a M2-1 protein of a mammalian MPV variant A2, wherein the M2-1 protein of a mammalian
- 25 MPV variant A2 is phylogenetically closer related to the M2-1 protein of the prototype of variant A2, isolate NL/17/00, than it is related to the M2-1 protein of the prototype of variant

B1, isolate NL/1/99, the M2-1 protein of the prototype of A1, isolate NL/1/00, or the M2-1 protein of the prototype of B2, isolate NL/1/94. The invention provides a M2-1 protein of a mammalian MPV variant A2, wherein the amino acid sequence of the M2-1 protein is at least 99%, or at least 99.5% identical to the M2-1 protein of a mammalian MPV variant A2 as represented by the prototype NL/17/00 (SEQ ID NO: 43). The invention provides a M2-2 protein of a mammalian MPV variant A2, wherein the M2-2 protein of a mammalian MPV variant A2 is phylogenetically closer related to the M2-2 protein of the prototype of variant A2, isolate NL/17/00, than it is related to the M2-2 protein of the prototype of variant B1,

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isolate NL/1/99, the M2-2 protein of the prototype of A1, isolate NL/1/00, or the M2-2 protein of the prototype of B2, isolate NL/1/94. The invention provides a M2-2 protein of a mammalian MPV variant A2, wherein the amino acid sequence of the M2-2 protein is at least 96%, at least 98%, at least 99% or at least 99.5% identical to the M2-2 protein of a mammalian MPV variant A2 as represented by the prototype NL/17/00 (SEQ ID NO:51).

The invention provides a SH protein of a mammalian MPV variant A2, wherein the SH protein of a mammalian MPV variant A2 is phylogenetically closer related to the SH protein of the prototype of variant A2, isolate NL/17/00, than it is related to the SH protein of the prototype of variant B1, isolate NL/1/99, the SH protein of the prototype of A1, isolate NL/1/00, or the SH protein of the prototype of B2, isolate NL/1/94. The invention provides a

SH protein of a mammalian MPV variant A2, wherein the amino acid sequence of the SH protein is at least 84%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99% or at least 99.5% identical to the SH protein of a mammalian MPV variant A2 as represented by the prototype NL/17/00 (SEQ ID NO:87). The invention provides a L protein of a mammalian MPV variant A2, wherein the L protein of a mammalian MPV variant A2 is phylogenetically closer related to the L protein of the prototype of variant A2, isolate NL/17/00, than it is related to the L protein of the prototype of variant B1, isolate NL/1/99, the L protein of the prototype of A1, isolate NL/1/00, or the L protein of the prototype of B2, isolate NL/1/94. The invention provides a L protein of a mammalian MPV variant A2, wherein the amino acid sequence of the L protein is at least 99% or at least 99.5% identical to the L protein of a mammalian MPV variant A2 as represented by the prototype NL/17/00 (SEQ ID NO:35).

The invention provides a G protein of a mammalian MPV variant B2, wherein the G protein of a mammalian MPV variant B2 is phylogenetically closer related to the G protein of the prototype of variant B2, isolate NL/1/94, than it is related to the G protein of the

5 prototype of variant B1, isolate NL/1/99, the G protein of the prototype of A1, isolate NL/1/00, or the G protein of the prototype of A2, isolate NL/17/00. The invention provides a G protein of a mammalian MPV variant B2, wherein the amino acid sequence of the G protein is at least 66%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% or at least 99.5% identical to the G protein of a

10 mammalian MPV variant B2 as represented by the prototype NL/1/94 (SEQ ID NO:29). The invention provides a N protein of a mammalian MPV variant B2, wherein the N protein of a mammalian MPV variant B2 is phylogenetically closer related to the N protein of the prototype of variant B2, isolate NL/1/94, than it is related to the N protein of the prototype of variant B1, isolate NL/1/99, the N protein of the prototype of A1, isolate NL/1/00, or the N

15 protein of the prototype of A2, isolate NL/17/00. The invention provides a N protein of a mammalian MPV variant B2, wherein the amino acid sequence of the N protein is at least 99% or at least 99.5% identical to the N protein of a mammalian MPV variant B2 as represented by the prototype NL/1/94 (SEQ ID NO:73). The invention provides a P protein of a mammalian MPV variant B2, wherein the P protein of a mammalian MPV variant B2 is

20 phylogenetically closer related to the P protein of the prototype of variant B2, isolate NL/1/94, than it is related to the P protein of the prototype of variant B1, isolate NL/1/99, the P protein of the prototype of A1, isolate NL/1/00, or the P protein of the prototype of A2, isolate NL/17/00. The invention provides a P protein of a mammalian MPV variant B2, wherein the amino acid sequence of the P protein is at least 96%, at least 98%, or at least

25 99% or at least 99.5% identical to the P protein of a mammalian MPV variant B2 as represented by the prototype NL/1/94 (SEQ ID NO:81). The invention provides a M protein of a mammalian MPV variant B2, wherein the M protein of a mammalian MPV variant B2 is phylogenetically closer related to the M protein of the prototype of variant B2, isolate NL/1/94, than it is related to the M protein of the prototype of variant B1, isolate NL/1/99,

30 the M protein of the prototype of A1, isolate NL/1/00, or the M protein of the prototype of A2, isolate NL/17/00. The invention provides a M protein of a mammalian MPV variant B2,

wherein the amino acid sequence of its M protein is identical to the M protein of a mammalian MPV variant B2 as represented by the prototype NL/1/94 (SEQ ID NO:65). The invention provides a F protein of a mammalian MPV variant B2, wherein the F protein of a mammalian MPV variant B2 is phylogenetically closer related to the F protein of the prototype of variant B2, isolate NL/1/94, than it is related to the F protein of the prototype of variant B1, isolate NL/1/99, the F protein of the prototype of A1, isolate NL/1/00, or the F protein of the prototype of A2, isolate NL/17/00. The invention provides a F protein of a mammalian MPV variant B2, wherein the amino acid sequence of the F protein is at least 99% or at least 99.5% identical to the F protein of a mammalian MPV variant B2 as represented by the prototype NL/1/94 (SEQ ID NO:21). The invention provides a M2-1 protein of a mammalian MPV variant B2, wherein the M2-1 protein of a mammalian MPV variant B2 is phylogenetically closer related to the M2-1 protein of the prototype of variant B2, isolate NL/1/94, than it is related to the M2-1 protein of the prototype of variant B1, isolate NL/1/99, the M2-1 protein of the prototype of A1, isolate NL/1/00, or the M2-1 protein of the prototype of A2, isolate NL/17/00. The invention provides a M2-1 protein of a mammalian MPV variant B2, wherein the amino acid sequence of the M2-1 protein is at least 98% or at least 99% or at least 99.5% identical to the M2-1 protein of a mammalian MPV variant B2 as represented by the prototype NL/1/94 (SEQ ID NO:45). The invention provides a M2-2 protein of a mammalian MPV variant B2, wherein the M2-2 protein of a mammalian MPV variant B2 is phylogenetically closer related to the M2-2 protein of the prototype of variant B2, isolate NL/1/94, than it is related to the M2-2 protein of the prototype of variant B1, isolate NL/1/99, the M2-2 protein of the prototype of A1, isolate NL/1/00, or the M2-2 protein of the prototype of A2, isolate NL/17/00. The invention provides a M2-2 protein of a mammalian MPV variant B2, wherein the amino acid sequence is at least 99% or at least 99.5% identical to the M2-2 protein of a mammalian MPV variant B2 as represented by the prototype NL/1/94 (SEQ ID NO:53). The invention provides a SH protein of a mammalian MPV variant B2, wherein the SH protein of a mammalian MPV variant B2 is phylogenetically closer related to the SH protein of the prototype of variant B2, isolate NL/1/94, than it is related to the SH protein of the prototype of variant B1, isolate NL/1/99, the SH protein of the prototype of A1, isolate NL/1/00, or the SH protein of the

prototype of A2, isolate NL/17/00. The invention provides a SH protein of a mammalian MPV variant B2, wherein the amino acid sequence of the SH protein is at least 84%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% or at least 99.5% identical to
5 the SH protein of a mammalian MPV variant B2 as represented by the prototype NL/1/94 (SEQ ID NO:89). The invention provides a L protein of a mammalian MPV variant B2, wherein the L protein of a mammalian MPV variant B2 is phylogenetically closer related to the L protein of the prototype of variant B2, isolate NL/1/94, than it is related to the L protein of the prototype of variant B1, isolate NL/1/99, the L protein of the prototype of A1, isolate
10 NL/1/00, or the L protein of the prototype of A2, isolate NL/17/00. The invention provides a L protein of a mammalian MPV variant B2, wherein the and/or if the amino acid sequence of the L protein is at least 99% or at least 99.5% identical to the L protein of a mammalian MPV variant B2 as represented by the prototype NL/1/94 (SEQ ID NO:37).

In certain embodiments, the percentage of sequence identity is based on an alignment
15 of the full length proteins. In other embodiments, the percentage of sequence identity is based on an alignment of contiguous amino acid sequences of the proteins, wherein the amino acid sequences can be 25 amino acids, 50 amino acids, 75 amino acids, 100 amino acids, 125 amino acids, 150 amino acids, 175 amino acids, 200 amino acids, 225 amino acids, 250 amino acids, 275 amino acids, 300 amino acids, 325 amino acids, 350 amino
20 acids, 375 amino acids, 400 amino acids, 425 amino acids, 450 amino acids, 475 amino acids, 500 amino acids, 750 amino acids, 1000 amino acids, 1250 amino acids, 1500 amino acids, 1750 amino acids, 2000 amino acids or 2250 amino acids in length.

The invention further provides nucleic acid sequences derived from a mammalian MPV. The invention also provides derivatives of nucleic acid sequences derived from a
25 mammalian MPV. In certain specific embodiments the nucleic acids are modified.

In certain embodiments, a nucleic acid of the invention encodes a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein of a mammalian MPV as defined above. In certain embodiments, a nucleic acid of the invention encodes a G protein, a N protein, a P protein, a M protein, a F protein, a
30 M2-1 protein, a M2-2 protein, a SH protein, or a L protein of subgroup A of a mammalian MPV as defined above. In a specific embodiment, the G gene of a mammalian MPV has the

nucleotide sequence of SEQ ID NO:98-132. In a specific embodiment, the F gene of a mammalian MPV has the nucleotide sequence of SEQ ID NO:168-247. In certain embodiments, a nucleic acid of the invention encodes a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein of subgroup B of a mammalian MPV as defined above. In certain embodiments, a nucleic acid of the invention encodes a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein of variant A1 of a mammalian MPV as defined above. In certain embodiments, a nucleic acid of the invention encodes a G protein, 5 a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein of variant A2 of a mammalian MPV as defined above. In certain embodiments, a nucleic acid of the invention encodes a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein of variant B1 of a mammalian MPV as defined above. In certain embodiments, a nucleic acid of the 10 invention encodes a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein of variant B2 of a mammalian MPV as defined above.

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In certain embodiments, the invention provides a nucleotide sequence that is at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to the nucleotide sequence of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97. In certain embodiments, the nucleic acid sequence of the invention, is at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% identical to a fragment of the nucleotide sequence of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97, wherein the fragment is at least 25 nucleotides, at least 50 nucleotides, at least 75 nucleotides, at least 100 nucleotides, at least 150 nucleotides, at least 200 nucleotides, at least 250 nucleotides, at least 300 nucleotides, at least 400 nucleotides, at least 500 nucleotides, at least 750 nucleotides, at least 1,000 nucleotides, at 20 least 1,250 nucleotides, at least 1,500 nucleotides, at least 1,750 nucleotides, at least 2,000 nucleotides, at least 2,000 nucleotides, at least 3,000 nucleotides, at least 4,000 nucleotides, at 25

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- least 5,000 nucleotides, at least 7,500 nucleotides, at least 10,000 nucleotides, at least 12,500 nucleotides, or at least 15,000 nucleotides in length. In a specific embodiment, the nucleic acid sequence of the invention is at least 50%, at least 55%, at least 60%, at least 65%, at 5 least 70%, at least 75%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% or 100% identical to one of the nucleotide sequences of SEQ ID NO:98-132; SEQ ID NO:168-247; SEQ ID NO:22-25; SEQ ID NO:30-33; SEQ ID NO:38-41; SEQ ID NO:46-49; SEQ ID NO:54-57; SEQ ID NO:58-61; SEQ ID NO:66-69; SEQ ID NO:74-77; SEQ ID NO:82-85; or SEQ ID NO:90-93.
- 10 In specific embodiments of the invention, a nucleic acid sequence of the invention is capable of hybridizing under low stringency, medium stringency or high stringency conditions to one of the nucleic acid sequences of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97. In specific embodiments of the invention, a nucleic acid sequence of the invention is capable of hybridizing under low stringency, medium stringency 15 or high stringency conditions to one of the nucleic acid sequences of SEQ ID NO:98-132; SEQ ID NO:168-247; SEQ ID NO:22-25; SEQ ID NO:30-33; SEQ ID NO:38-41; SEQ ID NO:46-49; SEQ ID NO:54-57; SEQ ID NO:58-61; SEQ ID NO:66-69; SEQ ID NO:74-77; SEQ ID NO:82-85; or SEQ ID NO:90-93. In certain embodiments, a nucleic acid hybridizes over a length of at least 25 nucleotides, at least 50 nucleotides, at least 75 nucleotides, at least 20 100 nucleotides, at least 150 nucleotides, at least 200 nucleotides, at least 250 nucleotides, at least 300 nucleotides, at least 400 nucleotides, at least 500 nucleotides, at least 750 nucleotides, at least 1,000 nucleotides, at least 1,250 nucleotides, at least 1,500 nucleotides, at least 1,750 nucleotides, at least 2,000 nucleotides, at least 2,00 nucleotides, at least 3,000 nucleotides, at least 4,000 nucleotides, at least 5,000 nucleotides, at least 7,500 nucleotides, 25 at least 10,000 nucleotides, at least 12,500 nucleotides, or at least 15,000 nucleotides with the nucleotide sequence of SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, or SEQ ID NO:97.

The invention further provides antibodies and antigen-binding fragments that bind specifically to a protein of a mammalian MPV. An antibody of the invention binds specifically to a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, 30 a M2-2 protein, a SH protein, or a L protein of a mammalian MPV. In specific embodiments, the antibody is a human antibody or a humanized antibody. In certain

embodiments, an antibody of the invention binds specifically to a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein of a virus of subgroup A of a mammalian MPV. In certain other embodiments, an antibody
5 of the invention binds specifically to a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein of a virus of subgroup B of a mammalian MPV. In certain, more specific, embodiments, an antibody of the invention binds specifically to a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein of a virus of variant A1 of a mammalian
10 MPV. In other embodiments, the antibody of the invention binds specifically to a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein of a virus of subgroup A2 of a mammalian MPV. In certain embodiments, an antibody of the invention binds specifically to a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein
15 of a virus of subgroup B1 of a mammalian MPV. In certain other embodiments, an antibody of the invention binds specifically to a G protein, a N protein, a P protein, a M protein, a F protein, a M2-1 protein, a M2-2 protein, a SH protein, or a L protein of a virus of subgroup B2 of a mammalian MPV.

20 **5.1.3. INSERTION OF THE HETEROLOGOUS GENE SEQUENCE**

Insertion of a foreign gene sequence into a viral vector of the invention can be accomplished by either a complete replacement of a viral coding region with a heterologous sequence, or by a partial replacement of the same, or by adding the heterologous nucleotide sequence to the viral genome. Complete replacement would probably best be accomplished
25 through the use of PCR-directed mutagenesis. Briefly, PCR-primer A would contain, from the 5' to 3' end: a unique restriction enzyme site, such as a class IIIS restriction enzyme site (*i.e.*, a "shifter" enzyme; that recognizes a specific sequence but cleaves the DNA either upstream or downstream of that sequence); a stretch of nucleotides complementary to a region of the PIV gene; and a stretch of nucleotides complementary to the carboxy-terminus
30 coding portion of the heterologous sequence. PCR-primer B would contain from the 5' to 3' end: a unique restriction enzyme site; a stretch of nucleotides complementary to a PIV gene;

and a stretch of nucleotides corresponding to the 5' coding portion of the foreign gene. After a PCR reaction using these primers with a cloned copy of the foreign gene, the product may be excised and cloned using the unique restriction sites. Digestion with the class II S enzyme
5 and transcription with the purified phage polymerase would generate an RNA molecule containing the exact untranslated ends of the PIV gene with a foreign gene insertion. In an alternate embodiment, PCR-primed reactions could be used to prepare double-stranded DNA containing the bacteriophage promoter sequence, and the hybrid gene sequence so that RNA templates can be transcribed directly without cloning.

10 A heterologous nucleotide sequence can be added or inserted at various positions of the virus of the invention. In one embodiment, the heterologous nucleotide sequence is added or inserted at position 1. In another embodiment, the heterologous nucleotide sequence is added or inserted at position 2. In another embodiment, the heterologous nucleotide sequence is added or inserted at position 3. In another embodiment, the
15 heterologous nucleotide sequence is added or inserted at position 4. In another embodiment, the heterologous nucleotide sequence is added or inserted at position 5. In yet another embodiment, the heterologous nucleotide sequence is added or inserted at position 6. As used herein, the term "position" refers to the position of the heterologous nucleotide sequence on the viral genome to be transcribed, e.g., position 1 means that it is the first gene to be transcribed, and position 2 means that it is the second gene to be transcribed. Inserting heterologous nucleotide sequences at the lower-numbered positions of the virus generally results in stronger expression of the heterologous nucleotide sequence compared to insertion at higher-numbered positions due to a transcriptional gradient that occurs across the genome of the virus. However, the transcriptional gradient also yields specific ratios of viral
20 mRNAs. Insertion of foreign genes will perturb these ratios and result in the synthesis of different amounts of viral proteins that may influence virus replication. Thus, both the transcriptional gradient and the replication kinetics must be considered when choosing an insertion site. For example, insertion of heterologous nucleotide sequence at position 2 of the b/h PIV3 vector results in the best replication rate and expression level of the
25 heterologous gene. Inserting heterologous nucleotide sequences at lower-numbered positions is the preferred embodiment of the invention if strong expression of the heterologous
30

nucleotide sequence is desired. In a preferred embodiment, the heterologous sequence is added or inserted at position 1, 2 or 3.

When inserting a heterologous nucleotide sequence into the virus of the invention, 5 the intergenic region between the end of the coding sequence of the heterologous gene and the start of the coding sequence of the downstream gene can be altered to achieve a desired effect. As used herein, the term "intergenic region" refers to nucleotide sequence between the stop signal of one gene and the start codon (*e.g.*, AUG) of the coding sequence of the next downstream open reading frame. An intergenic region may comprise a non-coding 10 region of a gene, *i.e.*, between the transcription start site and the start of the coding sequence (AUG) of the gene. This non-coding region occurs naturally in bPIV3 mRNAs and other viral genes, which is illustrated as non-limiting examples in Table 2:

Table 2: Lengths of Non-coding Regions for bPIV3 mRNAs

15	... CTT [Gene Start]	AUG ...
	N	45 nucleotides	
	P	68 nucleotides	
	M	21 nucleotides	
20	F	201 nucleotides	
	HN	62 nucleotides	
	L	12 nucleotides	
	b/h RSV F1	10 nucleotides	
	b/h RSV F2	86 nucleotides	
25	<u>b/h RSV F1 NP-P</u>	83 nucleotides	

In various embodiments, the intergenic region between the heterologous nucleotide sequence and the downstream gene can be engineered, independently from each other, to be at least 10 nt in length, at least 20 nt in length, at least 30 nt in length, at least 50 nt in length, 30 at least 75 nt in length, at least 100 nt in length, at least 125 nt in length, at least 150 nt in length, at least 175 nt in length or at least 200 nt in length. In certain embodiments, the

intergenic region between the heterologous nucleotide sequence and the downstream gene can be engineered, independently from each other, to be at most 10 nt in length, at most 20 nt in length, at most 30 nt in length, at most 50 nt in length, at most 75 nt in length, at most 100 nt in length, at most 125 nt in length, at most 150 nt in length, at most 175 nt in length or at most 200 nt in length. In various embodiments, the non-coding region of a desired gene in a virus genome can also be engineered, independently from each other, to be at least 10 nt in length, at least 20 nt in length, at least 30 nt in length, at least 50 nt in length, at least 75 nt in length, at least 100 nt in length, at least 125 nt in length, at least 150 nt in length, at least 175 nt in length or at least 200 nt in length. In certain embodiments, the non-coding region of a desired gene in a virus genome can also be engineered, independently from each other, to be at most 10 nt in length, at most 20 nt in length, at most 30 nt in length, at most 50 nt in length, at most 75 nt in length, at most 100 nt in length, at most 125 nt in length, at most 150 nt in length, at most 175 nt in length, at most 200 nt in length.

When inserting a heterologous nucleotide sequence, the positional effect and the intergenic region manipulation can be used in combination to achieve a desirable effect. For example, the heterologous nucleotide sequence can be added or inserted at a position selected from the group consisting of position 1, 2, 3, 4, 5, and 6, and the intergenic region between the heterologous nucleotide sequence and the next downstream gene can be altered (see Table 3). In an exemplary embodiment, hRSV F gene is inserted at position 1 of a b/h PIV3 vector, and the intergenic region between F gene and N gene (*i.e.*, the next downstream gene of F) is altered to 177 nucleotides. Many more combinations are encompassed by the present invention and some are shown by way of example in Table 3.

Table 3. Examples of mode of insertion of heterologous nucleotide sequences

	Position 1	Position 2	Position 3	Position 4	Position 5	Position 6
5	IGR ^a	10-20	10-20	10-20	10-20	10-20
	IGR	21-40	21-40	21-40	21-40	21-40
	IGR	41-60	41-60	41-60	41-60	41-60
	IGR	61-80	61-80	61-80	61-80	61-80
	IGR	81-100	81-100	81-100	81-100	81-100
	IGR	101-120	101-120	101-120	101-120	101-120
	IGR	121-140	121-140	121-140	121-140	121-140
	IGR	141-160	141-160	141-160	141-160	141-160
	IGR	161-180	161-180	161-180	161-180	161-180
	IGR	181-200	181-200	181-200	181-200	181-200
10	IGR	201-220	201-220	201-220	201-220	201-220
	IGR	221-240	221-240	221-240	221-240	221-240
	IGR	241-260	241-260	241-260	241-260	241-260
	IGR	261-280	261-280	261-280	261-280	261-280
	IGR	281-300	281-300	281-300	281-300	281-300
15						

^a Intergenic Region, measured in nucleotide.

Depending on the purpose (e.g., to have strong immunogenicity) of the inserted heterologous nucleotide sequence, the position of the insertion and the length of the intergenic region of the inserted heterologous nucleotide sequence can be determined by various indexes including, but not limited to, replication kinetics and protein or mRNA expression levels, measured by following non-limiting examples of assays: plaque assay, fluorescent-focus assay, infectious center assay, transformation assay, endpoint dilution assay, efficiency of plating, electron microscopy, hemagglutination, measurement of viral enzyme activity, viral neutralization, hemagglutination inhibition, complement fixation, immunostaining, immunoprecipitation and immunoblotting, enzyme-linked immunosorbent assay, nucleic acid detection (e.g., Southern blot analysis, Northern blot analysis, Western blot analysis), growth curve, employment of a reporter gene (e.g., using a reporter gene, such as Green Fluorescence Protein (GFP) or enhanced Green Fluorescence Protein (eGFP), integrated to the viral genome the same fashion as the interested heterologous gene to observe the protein expression), or a combination thereof. Procedures of performing these

assays are well known in the art (see, e.g., Flint et al., PRINCIPLES OF VIROLOGY, MOLECULAR BIOLOGY, PATHOGENESIS, AND CONTROL, 2000, ASM Press pp 25 - 56, the entire text is incorporated herein by reference), and non-limiting examples are given in the

5 Example sections, *infra*.

For example, expression levels can be determined by infecting cells in culture with a virus of the invention and subsequently measuring the level of protein expression by, e.g., Western blot analysis or ELISA using antibodies specific to the gene product of the heterologous sequence, or measuring the level of RNA expression by, e.g., Northern blot analysis using probes specific to the heterologous sequence. Similarly, expression levels of the heterologous sequence can be determined by infecting an animal model and measuring the level of protein expressed from the heterologous sequence of the recombinant virus of the invention in the animal model. The protein level can be measured by obtaining a tissue sample from the infected animal and then subjecting the tissue sample to Western blot analysis or ELISA, using antibodies specific to the gene product of the heterologous sequence. Further, if an animal model is used, the titer of antibodies produced by the animal against the gene product of the heterologous sequence can be determined by any technique known to the skilled artisan, including but not limited to, ELISA.

As the heterologous sequences can be homologous to a nucleotide sequence in the genome of the virus, care should be taken that the probes and the antibodies are indeed specific to the heterologous sequence or its gene product.

In certain specific embodiments, expression levels of F-protein of RSV or hMPV from chimeric b/h PIV3 RSV or b/h PIV3 hMPV or b/h PIV3 RSV F and hMPV F can be determined by any technique known to the skilled artisan. Expression levels of the F-protein can be determined by infecting cells in a culture with the chimeric virus of the invention and measuring the level of protein expression by, e.g., Western blot analysis or ELISA using antibodies specific to the F-protein and/or the G-protein of hMPV, or measuring the level of RNA expression by, e.g., Northern blot analysis using probes specific to the F-gene and/or the G-gene of human metapneumovirus. Similarly, expression levels of the heterologous sequence can be determined using an animal model by infecting an animal and measuring the level of F-protein and/or G-protein in the animal model. The protein level can be measured

- by obtaining a tissue sample from the infected animal and then subjecting the tissue sample to Western blot analysis or ELISA using antibodies specific to F-protein and/or G-protein of the heterologous sequence. Further, if an animal model is used, the titer of antibodies
- 5 produced by the animal against F-protein and/or G-protein can be determined by any technique known to the skilled artisan, including but not limited to, ELISA.

The rate of replication of a recombinant virus of the invention can be determined by any technique known to the skilled artisan.

- In certain embodiments, to facilitate the identification of the optimal position of the
- 10 heterologous sequence in the viral genome and the optimal length of the intergenic region, the heterologous sequence encodes a reporter gene. Once the optimal parameters are determined, the reporter gene is replaced by a heterologous nucleotide sequence encoding an antigen of choice. Any reporter gene known to the skilled artisan can be used with the methods of the invention. For more detail, see section 5.5.

- 15 The rate of replication of the recombinant virus can be determined by any standard technique known to the skilled artisan. The rate of replication is represented by the growth rate of the virus and can be determined by plotting the viral titer over the time post infection. The viral titer can be measured by any technique known to the skilled artisan. In certain embodiments, a suspension containing the virus is incubated with cells that are susceptible to
- 20 infection by the virus. Cell types that can be used with the methods of the invention include, but are not limited to, Vero cells, LLC-MK-2 cells, Hep-2 cells, LF 1043 (HEL) cells, MRC-5 cells, WI-38 cells, 293 T cells, QT 6 cells, QT 35 cells, chicken embryo fibroblast (CEF), or tMK cells. Subsequent to the incubation of the virus with the cells, the number of infected cells is determined. In certain specific embodiments, the virus comprises a reporter gene.
- 25 Thus, the number of cells expressing the reporter gene is representative of the number of infected cells. In a specific embodiment, the virus comprises a heterologous nucleotide sequence encoding for eGFP, and the number of cells expressing eGFP, *i.e.*, the number of cells infected with the virus, is determined using FACS.

- In certain embodiments, the replication rate of the recombinant virus of the invention
- 30 is at most 20 % of the replication rate of the wild type virus from which the recombinant virus is derived under the same conditions. The same conditions refer to the same initial titer

of virus, the same strain of cells, the same incubation temperature, growth medium, number of cells and other test conditions that may affect the replication rate. For example, the replication rate of b/h PIV3 with RSV's F gene in position 1 is at most 20 % of the 5 replication rate of bPIV3.

In certain embodiments, the replication rate of the recombinant virus of the invention is at most 5 %, at most 10 %, at most 20 %, at most 30 %, at most 40 %, at most 50 %, at most 75 %, at most 80 %, at most 90 % of the replication rate of the wild type virus from which the recombinant virus is derived under the same conditions. In certain embodiments, 10 the replication rate of the recombinant virus of the invention is at least 5 %, at least 10 %, at least 20 %, at least 30 %, at least 40 %, at least 50 %, at least 75 %, at least 80 %, at least 90 % of the replication rate of the wild type virus from which the recombinant virus is derived under the same conditions. In certain embodiments, the replication rate of the recombinant virus of the invention is between 5 % and 20 %, between 10 % and 40 %, 15 between 25 % and 50 %, between 40 % and 75 %, between 50 % and 80 %, or between 75 % and 90 % of the replication rate of the wild type virus from which the recombinant virus is derived under the same conditions.

In certain embodiments, the expression level of the heterologous sequence in the recombinant virus of the invention is at most 20 % of the expression level of the F-protein of 20 the wild type virus from which the recombinant virus is derived under the same conditions. The same conditions refer to the same initial titer of virus, the same strain of cells, the same incubation temperature, growth medium, number of cells and other test conditions that may affect the replication rate. For example, the expression level of the heterologous sequence of the F-protein of MPV in position 1 of bPIV3 is at most 20 % of the expression level of the 25 bovine F-protein of bPIV3.

In certain embodiments, the expression level of the heterologous sequence in the recombinant virus of the invention is at most 5 %, at most 10 %, at most 20 %, at most 30 %, at most 40 %, at most 50 %, at most 75 %, at most 80 %, at most 90 % of the expression 30 level of the F-protein of the wild type virus from which the recombinant virus is derived under the same conditions. In certain embodiments, the expression level of the heterologous sequence in the recombinant virus of the invention is at least 5 %, at least 10 %, at least 20

%, at least 30 %, at least 40 %, at least 50 %, at least 75 %, at least 80 %, at least 90 % of the expression level of the F-protein of the wild type virus from which the recombinant virus is derived under the same conditions. In certain embodiments, the expression level of the heterologous sequence in the recombinant virus of the invention is between 5 % and 20 %, between 10 % and 40 %, between 25 % and 50 %, between 40 % and 75 %, between 50 % and 80 %, or between 75 % and 90 % of the expression level of the F-protein of the wild type virus from which the recombinant virus is derived under the same conditions.

10 **5.1.4. INSERTION OF THE HETEROLOGOUS GENE SEQUENCE INTO
THE HN GENE**

The protein responsible for the hemagglutinin and neuraminidase activities of PIV are coded for by a single gene, HN. The HN protein is a major surface glycoprotein of the virus. For a variety of viruses, such as parainfluenza, the hemagglutinin and neuraminidase proteins have been shown to contain a number of antigenic sites. Consequently, this protein is a potential target for the humoral immune response after infection. Therefore, substitution of antigenic sites of HN with a portion of a foreign protein may provide for a vigorous humoral response against this foreign peptide. If a sequence is inserted within the HN molecule, and it is expressed on the outside surface of the HN, it will be immunogenic. For example, a peptide derived from gp160 of HIV could replace an antigenic site of the HN protein, resulting in a humoral immune response to both gp160 and the HN protein. In a different approach, the foreign peptide sequence may be inserted within the antigenic site without deleting any viral sequences. Expression products of such constructs may be useful in vaccines against the foreign antigen, and may indeed circumvent a problem discussed earlier, that of propagation of the recombinant virus in the vaccinated host. An intact HN molecule with a substitution only in antigenic sites may allow for HN function and thus allow for the construction of a viable virus. Therefore, this virus can be grown without the need for additional helper functions. The virus may also be attenuated in other ways to avoid any danger of accidental escape.

30 Other hybrid constructions may be made to express proteins on the cell surface or enable them to be released from the cell. As a surface glycoprotein, HN has an amino-

terminal cleavable signal sequence necessary for transport to the cell surface, and a carboxy-terminal sequence necessary for membrane anchoring. In order to express an intact foreign protein on the cell surface, it may be necessary to use these HN signals to create a hybrid 5 protein. In this case, the fusion protein may be expressed as a separate fusion protein from an additional internal promoter. Alternatively, if only the transport signals are present and the membrane anchoring domain is absent, the protein may be secreted out of the cell.

5.1.5. CONSTRUCTION OF BICISTRONIC RNA

10 Bicistronic mRNA could be constructed to permit internal initiation of translation of viral sequences and allow for the expression of foreign protein coding sequences from the regular terminal initiation site. Alternatively, a bicistronic mRNA sequence may be constructed wherein the viral sequence is translated from the regular terminal open reading frame, while the foreign sequence is initiated from an internal site. Certain internal ribosome entry site (IRES) sequences may be utilized. The IRES sequences that are chosen should be 15 short enough to avoid interference with parainfluenza packaging limitations. Thus, it is preferable that the IRES chosen for such a bicistronic approach be no more than 500 nucleotides in length, with less than 250 nucleotides being of ideal length. In a specific embodiment, the IRES is derived from a picornavirus and does not include any additional 20 picornaviral sequences. Preferred IRES elements include, but are not limited to, the mammalian BiP IRES and the hepatitis C virus IRES.

25 Alternatively, a foreign protein may be expressed from a new internal transcriptional unit in which the transcriptional unit has an initiation site and polyadenylation site. In another embodiment, the foreign gene is inserted into a PIV gene such that the resulting expressed protein is a fusion protein.

5.2. EXPRESSION OF HETEROLOGOUS GENE PRODUCTS USING RECOMBINANT cDNA AND RNA TEMPLATES

The recombinant templates prepared as described above can be used in a variety of ways to express the heterologous gene products in appropriate host cells or to create chimeric 30 viruses that express the heterologous gene products. In one embodiment, the recombinant cDNA can be used to transfect appropriate host cells and the resulting RNA may direct the

expression of the heterologous gene product at high levels. Host cell systems which provide for high levels of expression include continuous cell lines that supply viral functions such as cell lines superinfected with PIV, cell lines engineered to complement PIV functions, etc.

5 In an alternate embodiment of the invention, the recombinant templates may be used to transfect cell lines that express a viral polymerase protein in order to achieve expression of the heterologous gene product. To this end, transformed cell lines that express a polymerase protein such as the L protein may be utilized as appropriate host cells. Host cells may be similarly engineered to provide other viral functions or additional functions such as HN, NP
10 or N.

In another embodiment, a helper virus may provide the RNA polymerase protein utilized by the cells in order to achieve expression of the heterologous gene product. In yet another embodiment, cells may be transfected with vectors encoding viral proteins such as the N or NP, P, M2-1 and L proteins.

15 Different technique may be used to detect the expression of heterologous gene products (*see, e.g.*, Flint et al., PRINCIPLES OF VIROLOGY, MOLECULAR BIOLOGY, PATHOGENESIS, AND CONTROL, 2000, ASM Press pp 25 - 56, the entire text is incorporated herein by reference). In an exemplary assay, cells infected with the virus are permeabilized with methanol or acetone and incubated with an antibody raised against the heterologous
20 gene products. A second antibody that recognizes the first antibody is then added. This second antibody is usually conjugated to an indicator so that the expression of heterologous gene products may be visualized or detected.

5.3. RESCUE OF RECOMBINANT VIRUS PARTICLES

25 In order to prepare chimeric virus, modified cDNAs, virus RNAs, or RNA coding for the PIV genome and/or foreign proteins in the plus or minus sense may be used to transfect cells that provide viral proteins and functions required for replication and rescue. Alternatively, cells may be transfected with helper virus before, during, or after transfection by the DNA or RNA molecule coding for the PIV genome and/or foreign proteins. The
30 synthetic recombinant plasmid PIV DNAs and RNAs can be replicated and rescued into infectious virus particles by any number of techniques known in the art, as described in U.S.

Patent No. 5,166,057 issued November 24, 1992; in U.S. Patent No. 5,854,037 issued December 29, 1998; in European Patent Publication EP 0702085A1, published February 20, 1996; in U.S. Patent Application Serial No. 09/152,845; in International Patent Publications
5 PCT WO97/12032 published April 3, 1997; WO96/34625 published November 7, 1996; in European Patent Publication EP-A780475; WO 99/02657 published January 21, 1999; WO 98/53078 published November 26, 1998; WO 98/02530 published January 22, 1998; WO 99/15672 published April 1, 1999; WO 98/13501 published April 2, 1998; WO 97/06270 published February 20, 1997; and EPO 780 47SA1 published June 25, 1997, each of which is
10 incorporated by reference herein in its entirety.

In one embodiment of the present invention, synthetic recombinant viral RNAs that contain the non-coding regions of the negative strand virus RNA essential for the recognition by viral polymerases and for packaging signals necessary to generate a mature virion, may be prepared. There are a number of different approaches that may be used to apply the reverse
15 genetics approach to rescue negative strand RNA viruses. First, the recombinant RNAs are synthesized from a recombinant DNA template and reconstituted *in vitro* with purified viral polymerase complex to form recombinant ribonucleoproteins (RNPs) that can be used to transfect cells. In another approach, a more efficient transfection is achieved if the viral polymerase proteins are present during transcription of the synthetic RNAs either *in vitro* or
20 *in vivo*. With this approach the synthetic RNAs may be transcribed from cDNA plasmids that are either co-transcribed *in vitro* with cDNA plasmids encoding the polymerase proteins, or transcribed *in vivo* in the presence of polymerase proteins, *i.e.*, in cells which transiently or constitutively express the polymerase proteins.

In additional approaches described herein, the production of infectious chimeric virus
25 may be replicated in host cell systems that express a PIV viral polymerase protein (*e.g.*, in virus/host cell expression systems; transformed cell lines engineered to express a polymerase protein, etc.), so that infectious chimeric viruses are rescued. In this instance, helper virus need not be utilized since this function is provided by the viral polymerase proteins expressed.

30 In accordance with the present invention, any technique known to those of skill in the art may be used to achieve replication and rescue of recombinant and chimeric viruses. One

approach involves supplying viral proteins and functions required for replication *in vitro* prior to transfecting host cells. In such an embodiment, viral proteins may be supplied in the form of wild type virus, helper virus, purified viral proteins or recombinantly expressed viral 5 proteins. The viral proteins may be supplied prior to, during or post transcription of the synthetic cDNAs or RNAs encoding the chimeric virus. The entire mixture may be used to transfect host cells. In another approach, viral proteins and functions required for replication may be supplied prior to or during transcription of the synthetic cDNAs or RNAs encoding the chimeric virus. In such an embodiment, viral proteins and functions required for 10 replication are supplied in the form of wild type virus, helper virus, viral extracts, synthetic cDNAs or RNAs that express the viral proteins are introduced into the host cell via infection or transfection. This infection/transfection takes place prior to or simultaneous to the introduction of the synthetic cDNAs or RNAs encoding the chimeric virus.

In a particularly desirable approach, cells engineered to express all viral genes of the 15 recombinant or chimeric virus of the invention may result in the production of infectious chimeric virus that contain the desired genotype; thus eliminating the need for a selection system. Theoretically, one can replace any one of the six genes or part of any one of the six genes encoding structural proteins of PIV with a foreign sequence. However, a necessary part of this equation is the ability to propagate the defective virus (defective because a normal 20 viral gene product is missing or altered). A number of possible approaches are available to circumvent this problem. In one approach, a virus having a mutant protein can be grown in cell lines that are constructed to constitutively express the wild type version of the same protein. By this way, the cell line complements the mutation in the virus. Similar techniques may be used to construct transformed cell lines that constitutively express any of the PIV 25 genes. These cell lines which are made to express the viral protein may be used to complement the defect in the recombinant virus and thereby propagate it. Alternatively, certain natural host range systems may be available to propagate recombinant virus.

In yet another embodiment, viral proteins and functions required for replication may be supplied as genetic material in the form of synthetic cDNAs or RNAs so that they are co- 30 transcribed with the synthetic cDNAs or RNAs encoding the chimeric virus. In a particularly desirable approach, plasmids that express the chimeric virus and the viral polymerase and/or

other viral functions are co-transfected into host cells. For example, plasmids encoding the genomic or antigenomic PIV RNA, either wild type or modified, may be co-transfected into host cells with plasmids encoding the PIV viral polymerase proteins NP or N, P, M2-1 or L.

- 5 Alternatively, rescue of chimeric b/h PIV3 virus may be accomplished by the use of Modified Vaccinia Virus Ankara (MVA) encoding T7 RNA polymerase, or a combination of MVA and plasmids encoding the polymerase proteins (N, P, and L). For example, MVA-T7 or Fowl Pox-T7 can be infected into Vero cells, LLC-MK-2 cells, Hep-2 cells, LF 1043 (HEL) cells, tMK cells, LLC-MK2, HUT 292, FRHL-2 (rhesus), FCL-1 (green monkey), WI-38 10 (human), MRC-5 (human) cells, 293 T cells, QT 6 cells, QT 35 cells and CEF cells. After infection with MVA-T7 or Fowl Pox-T7, a full length antigenomic b/h PIV3 cDNA may be transfected into the HeLa or Vero cells together with the NP, P, M2-1 and L encoding expression plasmids. Alternatively, the polymerase may be provided by plasmid transfection. The cells and cell supernatant can subsequently be harvested and subjected to a single freeze- 15 thaw cycle. The resulting cell lysate may then be used to infect a fresh HeLa or Vero cell monolayer in the presence of 1-beta-D-arabinofuranosylcytosine (ara C), a replication inhibitor of vaccinia virus, to generate a virus stock. The supernatant and cells from these plates can then be harvested, freeze-thawed once, and the presence of bPIV3 virus particles detected by immunostaining of virus plaques using PIV3-specific antiserum.

- 20 Another approach to propagating the recombinant virus involves co-cultivation with wild-type virus. This could be done by simply taking recombinant virus and co-infecting cells with this and another wild-type virus (preferably a vaccine strain). The wild-type virus should complement for the defective virus gene product and allow growth of both the wild-type and recombinant virus. Alternatively, a helper virus may be used to support propagation 25 of the recombinant virus.

- In another approach, synthetic templates may be replicated in cells co-infected with recombinant viruses that express the PIV virus polymerase protein. In fact, this method may be used to rescue recombinant infectious virus in accordance with the invention. To this end, the PIV polymerase protein may be expressed in any expression vector/host cell system, 30 including but not limited to viral expression vectors (e.g., vaccinia virus, adenovirus, baculovirus, etc.) or cell lines that express a polymerase protein (e.g., see Krystal *et al.*, 1986,

Proc. Natl. Acad. Sci. USA 83: 2709-2713). Moreover, infection of host cells expressing all six PIV proteins may result in the production of infectious chimeric virus particles. It should be noted that it may be possible to construct a recombinant virus without altering virus 5 viability. These altered viruses would then be growth competent and would not need helper functions to replicate.

5.4. ATTENUATION OF RECOMBINANT VIRUSES

The recombinant viruses of the invention can be further genetically engineered to 10 exhibit an attenuated phenotype. In particular, the recombinant viruses of the invention exhibit an attenuated phenotype in a subject to which the virus is administered as a vaccine. Attenuation can be achieved by any method known to a skilled artisan. Without being bound by theory, the attenuated phenotype of the recombinant virus can be caused, *e.g.*, by using a virus that naturally does not replicate well in an intended host (*e.g.*, using a bovine PIV3 15 vector in human), by reduced replication of the viral genome, by reduced ability of the virus to infect a host cell, or by reduced ability of the viral proteins to assemble to an infectious viral particle relative to the wild type strain of the virus. The viability of certain sequences of the virus, such as the leader and the trailer sequence can be tested using a minigenome assay (see section 5.5.1).

20 The attenuated phenotypes of a recombinant virus of the invention can be tested by any method known to the artisan (see, *e.g.*, section 5.5). A candidate virus can, for example, be tested for its ability to infect a host or for the rate of replication in a cell culture system. In certain embodiments, a mini-genome system is used to test the attenuated virus when the gene that is altered is N, P, L, M2 or a combination thereof. In certain embodiments, growth 25 curves at different temperatures are used to test the attenuated phenotype of the virus. For example, an attenuated virus is able to grow at 35°C, but not at 39°C or 40°C. In certain embodiments, different cell lines can be used to evaluate the attenuated phenotype of the virus. For example, an attenuated virus may only be able to grow in monkey cell lines but not the human cell lines, or the achievable virus titers in different cell lines are different for 30 the attenuated virus. In certain embodiments, viral replication in the respiratory tract of a small animal model, including but not limited to, hamsters, cotton rats, mice and guinea pigs,

is used to evaluate the attenuated phenotypes of the virus. In other embodiments, the immune response induced by the virus, including but not limited to, the antibody titers (e.g., assayed by plaque reduction neutralization assay or ELISA) is used to evaluate the attenuated phenotypes of the virus. In a specific embodiment, the plaque reduction neutralization assay or ELISA is carried out at a low dose. In certain embodiments, the ability of the recombinant virus to elicit pathological symptoms in an animal model can be tested. A reduced ability of the virus to elicit pathological symptoms in an animal model system is indicative of its attenuated phenotype. In a specific embodiment, the candidate viruses are tested in a monkey model for nasal infection, indicated by mucous production.

The viruses of the invention can be attenuated such that one or more of the functional characteristics of the virus are impaired. In certain embodiments, attenuation is measured in comparison to the wild type strain of the virus from which the attenuated virus is derived. In other embodiments, attenuation is determined by comparing the growth of an attenuated virus in different host systems. Thus, for a non-limiting example, a bovine PIV3 is said to be attenuated when grown in a human host if the growth of the bovine PIV3 in the human host is reduced compared to the growth of the bovine PIV3 in a bovine host.

In certain embodiments, the attenuated virus of the invention is capable of infecting a host, is capable of replicating in a host such that infectious viral particles are produced. In comparison to the wild type strain, however, the attenuated strain grows to lower titers or grows more slowly. Any technique known to the skilled artisan can be used to determine the growth curve of the attenuated virus and compare it to the growth curve of the wild type virus. For exemplary methods see Example section, *infra*. In a specific embodiment, the attenuated virus grows to a titer of less than 10^5 pfu/ml, of less than 10^4 pfu/ml, of less than 10^3 pfu/ml, or of less than 10^2 pfu/ml in Vero cells under conditions as described.

In certain embodiments, the attenuated virus of the invention (e.g., a chimeric PIV3) cannot replicate in human cells as well as the wild type virus (e.g., wild type PIV3) does. However, the attenuated virus can replicate well in a cell line that lack interferon functions, such as Vero cells.

In other embodiments, the attenuated virus of the invention is capable of infecting a host, of replicating in the host, and of causing proteins of the virus of the invention to be

inserted into the cytoplasmic membrane, but the attenuated virus does not cause the host to produce new infectious viral particles. In certain embodiments, the attenuated virus infects the host, replicates in the host, and causes viral proteins to be inserted in the cytoplasmic

5 membrane of the host with the same efficiency as the wild type mammalian virus. In other embodiments, the ability of the attenuated virus to cause viral proteins to be inserted into the cytoplasmic membrane into the host cell is reduced compared to the wild type virus. In certain embodiments, the ability of the attenuated mammalian virus to replicate in the host is reduced compared to the wild type virus. Any technique known to the skilled artisan can be

10 used to determine whether a virus is capable of infecting a mammalian cell, of replicating within the host, and of causing viral proteins to be inserted into the cytoplasmic membrane of the host. For illustrative methods see section 5.5.

In certain embodiments, the attenuated virus of the invention is capable of infecting a host. In contrast to a wild type PIV, however, the attenuated PIV cannot be replicated in the

15 host. In a specific embodiment, the attenuated virus can infect a host and can cause the host to insert viral proteins in its cytoplasmic membranes, but the attenuated virus is incapable of being replicated in the host. Any method known to the skilled artisan can be used to test whether the attenuated virus has infected the host and has caused the host to insert viral proteins in its cytoplasmic membranes.

20 In certain embodiments, the ability of the attenuated mammalian virus to infect a host is reduced compared to the ability of the wild type virus to infect the same host. Any technique known to the skilled artisan can be used to determine whether a virus is capable of infecting a host. For illustrative methods see section 5.5.

In certain embodiments, mutations (*e.g.*, missense mutations) are introduced into the

25 genome of the virus to generate a virus with an attenuated phenotype. Mutations (*e.g.*, missense mutations) can be introduced into the N-gene, the P-gene, the F-gene, the M2-gene, the M2-1-gene, the M2-2-gene, the SH-gene, the G-gene or the L-gene of the recombinant virus. Mutations can be additions, substitutions, deletions, or combinations thereof. In specific embodiments, a single amino acid deletion mutation for the N, P, L or M2 proteins

30 are introduced, which can be screened for functionality in the mini-genome assay system and be evaluated for predicted functionality in the virus. In more specific embodiments, the

missense mutation is a cold-sensitive mutation. In other embodiments, the missense mutation is a heat-sensitive mutation. In one embodiment, major phosphorylation sites of P protein of the virus is removed. In another embodiment, a mutation or mutations are 5 introduced into the L gene of the virus to generate a temperature sensitive strain. In yet another embodiment, the cleavage site of the F gene is mutated in such a way that cleavage does not occur or occurs at very low efficiency.

In other embodiments, deletions are introduced into the genome of the recombinant virus. In more specific embodiments, a deletion can be introduced into the N-gene, the P- 10 gene, the F-gene, the M2-gene, the M2-1-gene, the M2-2-gene, the SH-gene, the G-gene or the L-gene of the recombinant virus. In specific embodiments, the deletion is in the M2-gene of the recombinant virus of the present invention. In other specific embodiments, the deletion is in the SH-gene of the recombinant virus of the present invention. In yet another specific embodiment, both the M2-gene and the SH-gene are deleted.

15 In certain embodiments, the intergenic region of the recombinant virus is altered. In one embodiment, the length of the intergenic region is altered. See Section 5.1.2. for illustrative examples. In another embodiment, the intergenic regions are shuffled from 5' to 3' end of the viral genome.

In other embodiments, the genome position of a gene or genes of the recombinant 20 virus is changed. In one embodiment, the F or G gene is moved to the 3' end of the genome. In another embodiment, the N gene is moved to the 5' end of the genome.

In certain embodiments, attenuation of the virus is achieved by replacing a gene of the wild type virus with a gene of a virus of a different species. In illustrative embodiments, the N-gene, the P-gene, the F-gene, the M2-gene, the M2-1-gene, the M2-2-gene, the SH-gene, 25 the HN-gene or the L-gene of bPIV3 is replaced with the N-gene, the P-gene, the F-gene, the M2-gene, the M2-1-gene, the M2-2-gene, the SH-gene, the HN-gene or the L-gene, respectively, of hPIV3. In other illustrative embodiments, the N-gene, the P-gene, the F-gene, the M2-gene, the M2-1-gene, the M2-2-gene, the SH-gene, the HN-gene or the L-gene 30 of hPIV3 is replaced with the N-gene, the P-gene, the F-gene, the M2-gene, the M2-1-gene, the M2-2-gene, the SH-gene, the HN-gene or the L-gene, respectively, of bPIV3. In a

preferred embodiment, attenuation of the virus is achieved by replacing one or more polymerase associated genes (e.g., N, P, L or M2) with genes of a virus of a different species.

- In certain embodiments, attenuation of the virus is achieved by replacing or deleting
- 5 one or more specific domains of a protein of the wild type virus with domains derived from the corresponding protein of a virus of a different species. In an illustrative embodiment, the ectodomain of a F protein of bPIV3 is replaced with an ectodomain of a F protein of a metapneumovirus. In a preferred embodiment, one or more specific domains of L, N, or P protein are replaced with domains derived from corresponding proteins of a virus of a
 - 10 different species. In another illustrative embodiment, the transmembrane domain of the F protein is deleted so that a soluble F protein is expressed.

- In certain embodiments of the invention, the leader and/or trailer sequence of the recombinant virus of the invention can be modified to achieve an attenuated phenotype. In certain, more specific embodiments, the leader and/or trailer sequence is reduced in length
- 15 relative to the wild type virus by at least 1 nucleotide, at least 2 nucleotides, at least 3 nucleotides, at least 4 nucleotides, at least 5 nucleotides or at least 6 nucleotides. In certain other, more specific embodiments, the sequence of the leader and/or trailer of the recombinant virus is mutated. In a specific embodiment, the leader and the trailer sequence are 100% complementary to each other. In other embodiments, 1 nucleotide, 2 nucleotides, 3
 - 20 nucleotides, 4 nucleotides, 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, or 10 nucleotides are not complementary to each other where the remaining nucleotides of the leader and the trailer sequences are complementary to each other. In certain embodiments, the non-complementary nucleotides are identical to each other. In certain other embodiments, the non-complementary nucleotides are different from each other.
 - 25 In other embodiments, if the non-complementary nucleotide in the trailer is purine, the corresponding nucleotide in the leader sequence is also a purine. In other embodiments, if the non-complementary nucleotide in the trailer is pyrimidine, the corresponding nucleotide in the leader sequence is also a purine.

- When a live attenuated vaccine is used, its safety must also be considered. The
- 30 vaccine must not cause disease. Any techniques known in the art that can make a vaccine safe may be used in the present invention. In addition to attenuation techniques, other

techniques may be used. One non-limiting example is to use a soluble heterologous gene that cannot be incorporated into the virion membrane. For example, a single copy of the soluble RSV F gene, a version of the RSV gene lacking the transmembrane and cytosolic domains,
5 can be used. Since it cannot be incorporated into the virion membrane, the virus tropism is not expected to change.

Various assays can be used to test the safety of a vaccine. See section 5.5., *infra*. Particularly, sucrose gradients and neutralization assays can be used. A sucrose gradient assay can be used to determine whether a heterologous protein is inserted in a virion. If the
10 heterologous protein is inserted in the virion, the virion should be tested for its ability to cause symptoms even if the parental strain does not cause symptoms. Without bound by theory, if the heterologous protein is incorporated in the virion, the virus may have acquired new, possibly pathological, properties.

15 **5.5. MEASUREMENT OF VIRAL TITER, EXPRESSION OF ANTIGENIC SEQUENCES, IMMUNOGENICITY AND OTHER CHARACTERISTICS OF CHIMERIC VIRUSES**

A number of assays may be employed in accordance with the present invention in order to determine the rate of growth of a chimeric or recombinant virus in a cell culture system, an animal model system or in a subject. A number of assays may also be employed
20 in accordance with the present invention in order to determine the requirements of the chimeric and recombinant viruses to achieve infection, replication and packaging of virions.

The assays described herein may be used to assay viral titre over time to determine the growth characteristics of the virus. In a specific embodiment, the viral titre is determined by obtaining a sample from the infected cells or the infected subject, preparing a serial dilution of the sample and infecting a monolayer of cells that are susceptible to infection with the virus at a dilution of the virus that allows for the emergence of single plaques. The
25 plaques can then be counted and the viral titre express as plaque forming units per milliliter of sample. In a specific embodiment of the invention, the growth rate of a virus of the invention in a subject is estimated by the titer of antibodies against the virus in the subject.
30 Without being bound by theory, the antibody titer in the subject reflects not only the viral

titer in the subject but also the antigenicity. If the antigenicity of the virus is constant, the increase of the antibody titer in the subject can be used to determine the growth curve of the virus in the subject. In a preferred embodiment, the growth rate of the virus in animals or
5 humans is best tested by sampling biological fluids of a host at multiple time points post-infection and measuring viral titer.

The expression of heterologous gene sequence in a cell culture system or in a subject can be determined by any technique known to the skilled artisan. In certain embodiments, the expression of the heterologous gene is measured by quantifying the level of the transcript.
10 The level of the transcript can be measured by Northern blot analysis or by RT-PCR using probes or primers, respectively, that are specific for the transcript. The transcript can be distinguished from the genome of the virus because the virus is in the antisense orientation whereas the transcript is in the sense orientation. In certain embodiments, the expression of the heterologous gene is measured by quantifying the level of the protein product of the
15 heterologous gene. The level of the protein can be measured by Western blot analysis using antibodies that are specific to the protein.

In a specific embodiment, the heterologous gene is tagged with a peptide tag. The peptide tag can be detected using antibodies against the peptide tag. The level of peptide tag detected is representative for the level of protein expressed from the heterologous gene.
20 Alternatively, the protein expressed from the heterologous gene can be isolated by virtue of the peptide tag. The amount of the purified protein correlates with the expression level of the heterologous gene. Such peptide tags and methods for the isolation of proteins fused to such a peptide tag are well known in the art. A variety of peptide tags known in the art may be used in the modification of the heterologous gene, such as, but not limited to, the
25 immunoglobulin constant regions, polyhistidine sequence (Petty, 1996, Metal-chelate affinity chromatography, in Current Protocols in Molecular Biology, volume 1-3 (1994-1998). Ed. by Ausubel, F.M., Brent, R., Kunston, R.E., Moore, D.D., Seidman, J.G., Smith, J.A. and Struhl, K. Published by John Wiley and sons, Inc., USA, Greene Publish. Assoc. & Wiley Interscience), glutathione S-transferase (GST; Smith, 1993, Methods Mol. Cell Bio. 4:220-
30 229), the *E. coli* maltose binding protein (Guan et al., 1987, Gene 67:21-30), various cellulose binding domains (U.S. patent 5,496,934; 5,202,247; 5,137,819; Tomme et al.,

1994, Protein Eng. 7:117-123), and the FLAG epitope (Short Protocols in Molecular Biology, 1999, Ed. Ausubel et al., John Wiley & Sons, Inc., Unit 10.11) etc. Other peptide tags are recognized by specific binding partners and thus facilitate isolation by affinity

5 binding to the binding partner, which is preferably immobilized and/or on a solid support. As will be appreciated by those skilled in the art, many methods can be used to obtain the coding region of the above-mentioned peptide tags, including but not limited to, DNA cloning, DNA amplification, and synthetic methods. Some of the peptide tags and reagents for their detection and isolation are available commercially.

10 Samples from a subject can be obtained by any method known to the skilled artisan. In certain embodiments, the sample consists of nasal aspirate, throat swab, sputum or broncho-alveolar lavage.

5.5.1. MINIGENOME CONSTRUCTS

15 Minireplicon constructs can be generated to contain an antisense reporter gene. Any reporter gene known to the skilled artisan can be used with the invention. In a specific embodiment, the reporter gene is CAT. In certain embodiments, the reporter gene can be flanked by the negative-sense bPIV or hPIV leader linked to the hepatitis delta ribozyme (Hep-d Ribo) and T7 polymerase termination (T-T7) signals, and the bPIV or hPIV trailer

20 sequence preceded by the T7 RNA polymerase promoter.

In certain embodiments, the plasmid encoding the minireplicon is transfected into a host cell. The host cell expresses T7 RNA polymerase, the N gene, the P gene, the L gene, and the M2.1 gene. In certain embodiments, the host cell is transfected with plasmids encoding T7 RNA polymerase, the N gene, the P gene, the L gene, and the M2.1 gene. In

25 other embodiments, the plasmid encoding the minireplicon is transfected into a host cell and the host cell is infected with a helper virus.

The expression level of the reporter gene and/or its activity can be assayed by any method known to the skilled artisan, such as, but not limited to, the methods described in section 5.5.6.

30 In certain, more specific, embodiments, the minireplicon comprises the following elements, in the order listed: T7 RNA Polymerase or RNA polymerase I, leader sequence,

gene start, GFP, trailer sequence, Hepatitis delta ribozyme sequence or RNA polymerase I termination sequence. If T7 is used as RNA polymerase, Hepatitis delta ribozyme sequence should be used as termination sequence. If RNA polymerase I is used, RNA polymerase I 5 termination sequence may be used as a termination signal. Dependent on the rescue system, the sequence of the minireplicon can be in the sense or antisense orientation. In certain embodiments, the leader sequence can be modified relative to the wild type leader sequence of the virus of the invention. The leader sequence can optionally be preceded by an AC. The T7 promoter sequence can be with or without a G-doublet or triplet, where the G-doublet or 10 triplet provides for increased transcription.

In a specific embodiment, a cell is infected with a virus of the invention at T0. 24 hours later, at T24, the cell is transfected with a minireplicon construct. 48 hours after T0 and 72 hours after T0, the cells are tested for the expression of the reporter gene. If a fluorescent reporter gene product is used (e.g., GFP), the expression of the reporter gene can 15 be tested using FACS.

In another embodiment, a cell is transfected with six plasmids at T=0 hours. Cells are then harvested at T=40 hours and T=60 hours and analyzed for CAT or GFP expression.

In another specific embodiment, a cell is infected with MVA-T7 at T0. 1 hour later, at T1, the cell is transfected with a minireplicon construct. 24 hours after T0, the cell is 20 infected with a virus of the invention. 72 hours after T0, the cells are tested for the expression of the reporter gene. If a fluorescent reporter gene product is used (e.g., GFP), the expression of the reporter gene can be tested using FACS.

5.5.2. MEASUREMENT OF INCIDENCE OF INFECTION RATE

The incidence of infection can be determined by any method well-known in the art, 25 including but not limited to, the testing of clinical samples (e.g., nasal swabs) for the presence of an infection, e.g., hMPV, RSV, hPIV, or bPIV/hPIV components can be detected by immunofluorescence assay (IFA) using an anti-hMPV-antigen antibody, an anti-RSV-antigen antibody, an anti-hPIV-antigen antibody, and/or an antibody that is specific to 30 the gene product of the heterologous nucleotide sequence, respectively.

In certain embodiments, samples containing intact cells can be directly processed,

whereas isolates without intact cells should first be cultured on a permissive cell line (e.g. HEp-2 cells). In an illustrative embodiment, cultured cell suspensions are cleared by centrifugation at, e.g., 300xg for 5 minutes at room temperature, followed by a PBS, pH 7.4

5 (Ca⁺⁺ and Mg⁺⁺ free) wash under the same conditions. Cell pellets are resuspended in a small volume of PBS for analysis. Primary clinical isolates containing intact cells are mixed with PBS and centrifuged at 300xg for 5 minutes at room temperature. Mucus is removed from the interface with a sterile pipette tip and cell pellets are washed once more with PBS under the same conditions. Pellets are then resuspended in a small volume of PBS for

10 analysis. Five to ten microliters of each cell suspension are spotted per 5 mm well on acetone washed 12-well HTC supercured glass slides and allowed to air dry. Slides are fixed in cold (-20°C) acetone for 10 minutes. Reactions are blocked by adding PBS - 1% BSA to each well followed by a 10 minute incubation at room temperature. Slides are washed three times in PBS - 0.1% Tween-20 and air dried. Ten microliters of each primary antibody

15 reagent diluted to 250 ng/ml in blocking buffer is spotted per well and reactions are incubated in a humidified 37°C environment for 30 minutes. Slides are then washed extensively in three changes of PBS - 0.1% Tween-20 and air dried. Ten microliters of appropriate secondary conjugated antibody reagent diluted to 250 ng/ml in blocking buffer are spotted per respective well and reactions are incubated in a humidified 37°C environment

20 for an additional 30 minutes. Slides are then washed in three changes of PBS - 0.1% Tween-20. Five microliters of PBS-50% glycerol-10 mM Tris pH 8.0-1 mM EDTA are spotted per reaction well and slides are mounted with cover slips. Each reaction well is subsequently analyzed by fluorescence microscopy at 200X power using a B-2A filter (EX 450-490 nm). Positive reactions are scored against an autofluorescent background obtained from unstained

25 cells or cells stained with secondary reagent alone. RSV positive reactions are characterized by bright fluorescence punctuated with small inclusions in the cytoplasm of infected cells.

5.5.3. MEASUREMENT OF SERUM TITER

Antibody serum titer can be determined by any method well-known in the art, for

30 example, but not limited to, the amount of antibody or antibody fragment in serum samples can be quantitated by a sandwich ELISA. Briefly, the ELISA consists of coating microtiter

plates overnight at 4°C with an antibody that recognizes the antibody or antibody fragment in the serum. The plates are then blocked for approximately 30 minutes at room temperature with PBS-Tween-0.5% BSA. Standard curves are constructed using purified antibody or

5 antibody fragment diluted in PBS-BSA-BSA, and samples are diluted in PBS-BSA. The samples and standards are added to duplicate wells of the assay plate and are incubated for approximately 1 hour at room temperature. Next, the non-bound antibody is washed away with PBS-TWEEN and the bound antibody is treated with a labeled secondary antibody (e.g., horseradish peroxidase conjugated goat-anti-human IgG) for approximately 1 hour at room

10 temperature. Binding of the labeled antibody is detected by adding a chromogenic substrate specific for the label and measuring the rate of substrate turnover, e.g., by a spectrophotometer. The concentration of antibody or antibody fragment levels in the serum is determined by comparison of the rate of substrate turnover for the samples to the rate of substrate turnover for the standard curve.

15

5.5.4. CHALLENGE STUDIES

This assay is used to determine the ability of the recombinant viruses of the invention and of the vaccines of the invention to prevent lower respiratory tract viral infection in an animal model system, including but not limited to, cotton rats, Syrian Golden hamsters, and

20 Balb/c mice. The recombinant virus and/or the vaccine can be administered by intravenous (IV) route, by intramuscular (IM) route or by intranasal route (IN). The recombinant virus and/or the vaccine can be administered by any technique well-known to the skilled artisan. This assay is also used to correlate the serum concentration of antibodies with a reduction in lung titer of the virus to which the antibodies bind.

25 On day 0, groups of animals, including but not limited to, cotton rats (*Sigmodon hispidus*, average weight 100 g) and hamsters (e.g., Syrian Golden hamsters) are inoculated with the recombinant virus or the vaccine of interest or BSA by intramuscular injection, by intravenous injection, or by intranasal route. Prior to, concurrently with, or subsequent to administration of the recombinant virus or the vaccine of the invention, the animals are

30 infected with wild type virus wherein the wild type virus is the virus against which the vaccine was generated. In certain embodiments, the animals are infected with the wild type

virus at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 1 week, at least 2 weeks, at least 3 weeks or at least 4 weeks subsequent to the administration of the recombinant virus and/or the vaccine of the invention. In a preferred embodiment, the animals are infected with the wild type virus 21 days subsequent to the administration of the recombinant virus and/or the vaccine of the invention. In another preferred embodiment, the animals are infected with the wild type virus 28 days subsequent to the administration of the recombinant virus and/or the vaccine of the invention.

After the infection, the animals are sacrificed, and their nasal turbinate tissue and/or lung tissue are harvested and virus titers are determined by appropriate assays, e.g., plaque assay and TCID₅₀ assay. Bovine serum albumin (BSA) 10 mg/kg can be used as a negative control. Antibody concentrations in the serum at the time of challenge can be determined using a sandwich ELISA.

15 5.5.5. CLINICAL TRIALS

Vaccines of the invention or fragments thereof that have been tested in *in vitro* assays and animal models may be further evaluated for safety, tolerance, immunogenicity, infectivity and pharmacokinetics in groups of normal healthy human volunteers, including all age groups. In a preferred embodiment, the healthy human volunteers are infants at about 6 weeks of age or older, children and adults. The volunteers are administered intranasally, intramuscularly, intravenously or by a pulmonary delivery system in a single dose of a recombinant virus of the invention and/or a vaccine of the invention. Multiple doses of virus and/or vaccine of the invention may be required in seronegative children 6 to 60 months of age. Multiple doses of virus and/or vaccine of the invention may also be required in the first six months of life to stimulate local and systemic immunity and to overcome neutralization by maternal antibody. In a preferred embodiment, a primary dosing regimen at 2, 4, and 6 months of age and a booster dose at the beginning of the second year of life are used. A recombinant virus of the invention and/or a vaccine of the invention can be administered alone or concurrently with pediatric vaccines recommended at the corresponding ages.

30 In a preferred embodiment, double-blind randomized, placebo-controlled clinical trials are used. In a specific embodiment, a computer generated randomization schedule is

used. For example, each subject in the study will be enrolled as a single unit and assigned a unique case number. Multiple subjects within a single family will be treated as individuals for the purpose of enrollment. Parent/guardian, subjects, and investigators will remain

5 blinded to which treatment group subjects have been assigned for the duration of the study. Serologic and virologic studies will be performed by laboratory personnel blinded to treatment group assignment. However, it is expected that isolation of the vaccine virus from nasal wash fluid obtained after vaccination will identify likely vaccinees to the virology laboratory staff. The serologic and virologic staff are separate and the serology group will be

10 prevented from acquiring any knowledge of the culture results.

Each volunteer is preferably monitored for at least 12 hours prior to receiving the recombinant virus of the invention and/or a vaccine of the invention, and each volunteer will be monitored for at least fifteen minutes after receiving the dose at a clinical site. Then volunteers are monitored as outpatients on days 1-14, 21, 28, 35, 42, 49, and 56 postdose. In

15 a preferred embodiment, the volunteers are monitored for the first month after each vaccination as outpatients. All vaccine related serious adverse events will be reported for the entire duration of the trial. A serious adverse event is defined as an event that 1) results in death, 2) is immediately life threatening, 3) results in permanent or substantial disability, 4) results in or prolongs an existing in-patient hospitalization, 5) results in a congenital

20 anomaly, 6) is a cancer, or 7) is the result of an overdose of the study vaccine. Serious adverse events that are not vaccine related will be reported beginning on the day of the first vaccination (Day 0) and continue for 30 days following the last vaccination. Non-vaccine related serious adverse events will not be reported for 5 to 8 months after the 30 day reporting period following the last vaccination. A dose of vaccine/placebo will not be given

25 if a child has a vaccine-related serious adverse event following the previous dose. Any adverse event that is not considered vaccine related, but which is of concern, will be discussed by the clinical study monitor and the medical monitor before the decision to give another dose is made.

Blood samples are collected via an indwelling catheter or direct venipuncture (e.g., by

30 using 10 ml red-top Vacutainer tubes) at the following intervals: (1) prior to administering the dose of the recombinant virus of the invention and/or a vaccine of the invention; (2)

during the administration of the dose of the recombinant virus of the invention and/or a vaccine of the invention; (3) 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, and 48 hours after administering the dose
5 of the recombinant virus of the invention and/or a vaccine of the invention; and (4) 3 days, 7 days 14 days, 21 days, 28 days, 35 days, 42 days, 49 days, and 56 days after administering the dose of the recombinant virus of the invention and/or a vaccine of the invention. In a specific embodiment, a total of 5 blood draws (3-5 ml each) are obtained, each just prior to the first, third and booster doses and approximately one month following the third dose and booster
10 dose of administration of the vaccine or placebo. Samples are allowed to clot at room temperature and the serum is collected after centrifugation.

Sera are tested for strain-specific serum hemagglutination inhibition (HAI) antibody levels against the virus of the invention. Other indicators of immunogenicity such as IgG, IgA, or neutralizing antibodies are also tested. Serum antibody responses to one or more of
15 the other vaccines given concurrently may be measured. The amount of antibodies generated against the recombinant virus of the invention and/or a vaccine of the invention in the samples from the patients can be quantitated by ELISA.

The concentration of antibody levels in the serum of volunteers are corrected by subtracting the predose serum level (background level) from the serum levels at each
20 collection interval after administration of the dose of recombinant virus of the invention and/or a vaccine of the invention. For each volunteer the pharmacokinetic parameters are computed according to the model-independent approach (Gibaldi *et al.*, eds., 1982, *Pharmacokinetics*, 2nd edition, Marcel Dekker, New York) from the corrected serum antibody or antibody fragment concentrations.

25 Nasal washes obtained approximately 2, 3, 4, 5, 6, 7 or 8 days after each doses of vaccine/placebo will be cultured to detect shedding of the vaccine virus of the invention. In a preferred embodiment, nasal washes obtained 7 days after each doses of vaccine/placebo are cultured. A nasopharyngeal swab, a throat swab, or a nasal wash is also used to determine the presence of other viruses in volunteers with medically attended febrile illness (rectal
30 temperature greater than or equal to 102° F) and/or croup, bronchiolitis, or pneumonia at any time during the study. Samples are shipped on dry ice to designated site for study. Assays

for isolation and quantitation of the vaccine virus of the invention and immunostaining assays using MAb to identify the vaccine virus of the invention are used (examples of such assays are given in the Example sections, *infra*). Nasal wash specimens may be tested for 5 other viruses and immune responses including IgG, IgA, and neutralizing antibody.

5.5.6. REPORTER GENES

In certain embodiments, assays for measurement of reporter gene expression in tissue culture or in animal models can be used with the methods of the invention. The nucleotide 10 sequence of the reporter gene is cloned into the virus, such as bPIV, hPIV, or b/hPIV3, wherein (i) the position of the reporter gene is changed and (ii) the length of the intergenic regions flanking the reporter gene are varied. Different combinations are tested to determine the optimal rate of expression of the reporter gene and the optimal replication rate of the virus comprising the reporter gene.

15 In certain embodiments, minigenome constructs are generated to include a reporter gene. The construction of minigenome constructs is described in section 5.5.1.

The abundance of the reporter gene product can be determined by any technique known to the skilled artisan. Such techniques include, but are not limited to, Northern blot analysis or Western blot analysis using probes or antibodies, respectively, that are specific to 20 the reporter gene.

In certain embodiments, the reporter gene emits a fluorescent signal that can be detected in a FACS. FACS can be used to detect cells in which the reporter gene is expressed.

Techniques for practicing the specific aspect of this invention will employ, unless 25 otherwise indicated, conventional techniques of molecular biology, microbiology, and recombinant DNA manipulation and production, which are routinely practiced by one of skill in the art. See, e.g., Sambrook, 1989, Molecular Cloning, A Laboratory Manual, Second Edition; DNA Cloning, Volumes I and II (Glover, Ed. 1985); and Transcription and Translation (Hames & Higgins, Eds. 1984).

30 The biochemical activity of the reporter gene product represents the expression level of the reporter gene. The total level of reporter gene activity depends also on the replication

rate of the recombinant virus of the invention. Thus, to determine the true expression level of the reporter gene from the recombinant virus, the total expression level should be divided by the titer of the recombinant virus in the cell culture or the animal model.

5 Reporter genes that can be used with the methods of invention include, but are not limited to, the genes listed in the Table 4 below:

Table 4: Reporter genes and the biochemical properties of the respective reporter gene products

	Reporter Gene	Protein Activity & Measurement
10	CAT (chloramphenicol acetyltransferase)	Transfers radioactive acetyl groups to chloramphenicol or detection by thin layer chromatography and autoradiography
	GAL (β -galactosidase)	Hydrolyzes colorless galactosides to yield colored products.
15	GUS (β -glucuronidase)	Hydrolyzes colorless glucuronides to yield colored products.
	LUC (luciferase)	Oxidizes luciferin, emitting photons
	GFP (green fluorescent protein)	fluorescent protein without substrate
20	SEAP (secreted alkaline phosphatase)	luminescence reaction with suitable substrates or with substrates that generate chromophores
	HRP (horseradish peroxidase)	in the presence of hydrogen oxide, oxidation of 3,3',5,5'-tetramethylbenzidine to form a colored complex
25	AP (alkaline phosphatase)	luminescence reaction with suitable substrates or with substrates that generate chromophores

30 The abundance of the reporter gene can be measured by, *inter alia*, Western blot analysis or Northern blot analysis or any other technique used for the quantification of transcription of a nucleotide sequence, the abundance of its mRNA its protein (see Short

Protocols in Molecular Biology, Ausubel *et al.* (editors), John Wiley & Sons, Inc., 4th edition, 1999). In certain embodiments, the activity of the reporter gene product is measured as a readout of reporter gene expression from the recombinant virus. For the quantification of the 5 activity of the reporter gene product, biochemical characteristics of the reporter gene product can be investigated (see Table 1). The methods for measuring the biochemical activity of the reporter gene products are well-known to the skilled artisan. A more detailed description of illustrative reporter genes that can be used with the methods of the invention is set forth below.

10

LUCIFERASE

Luciferases are enzymes that emit light in the presence of oxygen and a substrate (luciferin) and which have been used for real-time, low-light imaging of gene expression in cell cultures, individual cells, whole organisms, and transgenic organisms (reviewed by Greer 15 & Szalay, 2002, Luminescence 17(1):43-74).

As used herein, the term "luciferase" as used in relation to the invention is intended to embrace all luciferases, or recombinant enzymes derived from luciferases that have luciferase activity. The luciferase genes from fireflies have been well characterized, for example, from the *Photinus* and *Luciola* species (see, e.g., International Patent Publication No. WO 20 95/25798 for *Photinus pyralis*, European Patent Application No. EP 0 524 448 for *Luciola cruciata* and *Luciola lateralis*, and Devine *et al.*, 1993, Biochim. Biophys. Acta 1173(2):121-132 for *Luciola mingrelica*. Other eucaryotic luciferase genes include, but are not limited to, the sea panzy (*Renilla reniformis*, see, e.g., Lorenz *et al.*, 1991, Proc Natl Acad Sci U S A 88(10):4438-4442), and the glow worm (*Lampyris noctiluca*, see e.g., Sula-Newby *et al.*, 25 1996, Biochem J. 313:761-767). Bacterial luciferin-luciferase systems include, but are not limited to, the bacterial lux genes of terrestrial *Photorhabdus luminescens* (see, e.g., Manukhov *et al.*, 2000, Genetika 36(3):322-30) and marine bacteria *Vibrio fischeri* and *Vibrio harveyi* (see, e.g., Miyamoto *et al.*, 1988, J Biol Chem. 263(26):13393-9, and Cohn *et al.*, 1983, Proc Natl Acad Sci USA., 80(1):120-3, respectively). The luciferases 30 encompassed by the present invention also includes the mutant luciferases described in U.S. Patent No. 6,265,177 to Squirrell *et al.*, which is hereby incorporated by reference in its entirety.

GREEN FLUORESCENT PROTEIN

Green fluorescent protein ("GFP") is a 238 amino acid protein with amino acids 65 to 67 involved in the formation of the chromophore that does not require additional substrates or cofactors to fluoresce (see, e.g., Prasher *et al.*, 1992, Gene 111:229-233; Yang *et al.*, 1996, Nature Biotechnol. 14:1252-1256; and Cody *et al.*, 1993, Biochemistry 32:1212-1218).

As used herein, the term "green fluorescent protein" or "GFP" as used in relation to the invention is intended to embrace all GFPs (including the various forms of GFPs that exhibit colors other than green), or recombinant enzymes derived from GFPs that have GFP activity. The native gene for GFP was cloned from the bioluminescent jellyfish *Aequorea victoria* (see, e.g., Morin *et al.*, 1972, J. Cell Physiol. 77:313-318). Wild type GFP has a major excitation peak at 395 nm and a minor excitation peak at 470 nm. The absorption peak at 470 nm allows the monitoring of GFP levels using standard fluorescein isothiocyanate (FITC) filter sets. Mutants of the GFP gene have been found useful to enhance expression and to modify excitation and fluorescence. For example, mutant GFPs with alanine, glycine, isoleucine, or threonine substituted for serine at position 65 result in mutant GFPs with shifts in excitation maxima and greater fluorescence than wild type protein when excited at 488 nm (see, e.g., Heim *et al.*, 1995, Nature 373:663-664); U.S. Patent No. 5,625,048; Delagrange *et al.*, 1995, Biotechnology 13:151-154; Cormack *et al.*, 1996, Gene 173:33-38; and Cramer *et al.*, 1996, Nature Biotechnol. 14:315-319). The ability to excite GFP at 488 nm permits the use of GFP with standard fluorescence activated cell sorting ("FACS") equipment. In another embodiment, GFPs are isolated from organisms other than the jellyfish, such as, but not limited to, the sea pansy, *Renilla reniformis*.

EGFP is a red-shifted variant of wild-type GFP (3-5) which has been optimized for brighter fluorescence and higher expression in mammalian cells. (Excitation maximum = 488 nm; emission maximum = 507 nm.) EGFP encodes the GFPmut1 variant which contains the double-amino-acid substitution of Phe-64 to Leu and Ser-65 to Thr. The coding sequence of the EGFP gene contains more than 190 silent base changes which correspond to human codon-usage preferences.

BETA GALACTOSIDASE

Beta galactosidase (" β -gal") is an enzyme that catalyzes the hydrolysis of β -galactosides, including lactose, and the galactoside analogs o-nitrophenyl- β -D-galactopyranoside ("ONPG") and chlorophenol red- β -D-galactopyranoside ("CPRG") (see, e.g., Nielsen *et al.*, 1983 Proc Natl Acad Sci USA 80(17):5198-5202; Eustice *et al.*, 1991, Biotechniques 11:739-742; and Henderson *et al.*, 1986, Clin. Chem. 32:1637-1641). The β -gal gene functions well as a reporter gene because the protein product is extremely stable, resistant to proteolytic degradation in cellular lysates, and easily assayed. When ONPG is used as the substrate, β -gal activity can be quantitated with a spectrophotometer or a microplate reader.

As used herein, the term "beta galactosidase" or " β -gal" as used in relation to the invention is intended to embrace all β -gals, including *lacZ* gene products, or recombinant enzymes derived from β -gals which have β -gal activity. The β -gal gene functions well as a reporter gene because the protein product is extremely stable, resistant to proteolytic degradation in cellular lysates, and easily assayed. In an embodiment where ONPG is the substrate, β -gal activity can be quantitated with a spectrophotometer or microplate reader to determine the amount of ONPG converted at 420 nm. In an embodiment when CPRG is the substrate, β -gal activity can be quantitated with a spectrophotometer or microplate reader to determine the amount of CPRG converted at 570 to 595 nm.

CHLORAMPHENICOL ACETYLTRANSFERASE

Chloramphenicol acetyl transferase ("CAT") is commonly used as a reporter gene in mammalian cell systems because mammalian cells do not have detectable levels of CAT activity. The assay for CAT involves incubating cellular extracts with radiolabeled chloramphenicol and appropriate co-factors, separating the starting materials from the product by, for example, thin layer chromatography ("TLC"), followed by scintillation counting (see, e.g., U.S. Patent No. 5,726,041, which is hereby incorporated by reference in its entirety).

As used herein, the term "chloramphenicol acetyltransferase" or "CAT" as used in relation to the invention is intended to embrace all CATs, or recombinant enzymes derived from CAT which have CAT activity. While it is preferable that a reporter system which does

not require cell processing, radioisotopes, and chromatographic separations would be more amenable to high through-put screening, CAT as a reporter gene may be preferable in situations when stability of the reporter gene is important. For example, the CAT reporter 5 protein has an *in vivo* half life of about 50 hours, which is advantageous when an accumulative versus a dynamic change type of result is desired.

SECRETED ALKALINE PHOSPHATASE

The secreted alkaline phosphatase ("SEAP") enzyme is a truncated form of alkaline 10 phosphatase, in which the cleavage of the transmembrane domain of the protein allows it to be secreted from the cells into the surrounding media.

As used herein, the term "secreted alkaline phosphatase" or "SEAP" as used in relation to the invention is intended to embrace all SEAP or recombinant enzymes derived from SEAP which have alkaline phosphatase activity. SEAP activity can be detected by a 15 variety of methods including, but not limited to, measurement of catalysis of a fluorescent substrate, immunoprecipitation, HPLC, and radiometric detection. The luminescent method is preferred due to its increased sensitivity over calorimetric detection methods. The advantages of using SEAP is that a cell lysis step is not required since the SEAP protein is secreted out of the cell, which facilitates the automation of sampling and assay procedures. 20 A cell-based assay using SEAP for use in cell-based assessment of inhibitors of the Hepatitis C virus protease is described in U.S. Patent No. 6,280,940 to Potts *et al.* which is hereby incorporated by reference in its entirety.

5.5.7. CELL CULTURE SYSTEMS, EMBRYONATED EGGS, AND ANIMAL MODELS

25

Cell culture systems known in the art can be used to propagate or test activities of the viruses of the present invention. (See e.g., Flint *et al.*, PRINCIPLES OF VIROLOGY, MOLECULAR BIOLOGY, PATHOGENESIS, AND CONTROL, 2000, ASM Press pp25-29, the entire text is incorporated herein by reference). Examples of such cell culture systems 30 include, but are not limited to, primary cell culture that are prepared from animal tissues (e.g., cell cultures derived from monkey kidney, human embryonic amnion, kidney, and foreskin, and chicken or mouse embryos); diploid cell strains that consist of a homogeneous

- population of a single type and can divide up to 100 times before dying (e.g., cell culture derived from human embryos, such as the WI-38 strain derived from human embryonic lung); and continuous cell lines consist of a single cell type that can be propagated indefinitely in culture (e.g., HEp-2 cells, Hela cells, Vero cells, L and 3T3 cells, and BHK-21 cells).

Viruses of the invention can also be propagated in embryonated chicken eggs. At 5 to 14 days after fertilization, a hole is drilled in the shell and virus is injected into the site appropriate for its replication.

- 10 Any animal models known in the art can be used in the present invention to accomplish various purposes, such as to determine the effectiveness and safeness of vaccines of the invention. Examples of such animal models include, but are not limited to, cotton rats (*Sigmodon hispidus*), hamsters, mice, monkeys, and chimpanzees. In a preferred embodiment, Syrian Golden hamsters are used.

15

5.5.8. NEUTRALIZATION ASSAY

- Neutralization assays can be carried out to address the important safety issue of whether the heterologous surface glycoproteins are incorporated into the virion which may result in an altered virus tropism phenotype. As used herein, the term "tropism" refers to the 20 affinity of a virus for a particular cell type. Tropism is usually determined by the presence of cell receptors on specific cells which allow a virus to enter that and only that particular cell type. A neutralization assay is performed by using either MAbs of the heterologous surface glycoprotein (non-limiting example is the F protein of a negative strand RNA virus) or polyclonal antiserum comprising antibodies against the heterologous surface glycoprotein.
- 25 Different dilution of the antibodies are tested to see whether the chimeric virus of the invention can be neutralized. The heterologous surface glycoprotein should not be present on the virion surface in an amount sufficient to result in antibody binding and neutralization.

5.5.9. SUCROSE GRADIENT ASSAY

- 30 The question of whether the heterologous proteins are incorporated into the virion can be further investigated by use of a biochemical assay. Infected cell lysates can be fractionated in 20 - 60% sucrose gradients, various fractions are collected and analyzed for

the presence and distribution of heterologous proteins and the vector proteins by Western blot. The fractions and the virus proteins can also be assayed for peak virus titers by plaque assay. Examples of sucrose gradient assay are given in section 23, *infra*. When the
5 heterologous proteins are associated with the virion, they will co-migrate with the virion.

5.6. VACCINE FORMULATIONS USING THE CHIMERIC VIRUSES

The invention encompasses vaccine formulations comprising the engineered negative strand RNA virus of the present invention. The recombinant PIV viruses of the present
10 invention may be used as a vehicle to express foreign epitopes that induce a protective response to any of a variety of pathogens. In a specific embodiment, the invention encompasses the use of recombinant bPIV viruses or attenuated hPIV that have been modified in vaccine formulations to confer protection against hPIV infection.

The vaccine preparations of the invention encompass multivalent vaccines, including
15 bivalent and trivalent vaccine preparations. The bivalent and trivalent vaccines of the invention may be administered in the form of one PIV vector expressing each heterologous antigenic sequence or two or more PIV vectors each encoding different heterologous antigenic sequences. For example, a first chimeric PIV expressing one or more heterologous antigenic sequences can be administered in combination with a second chimeric PIV
20 expressing one or more heterologous antigenic sequences, wherein the heterologous antigenic sequences in the second chimeric PIV are different from the heterologous antigenic sequences in the first chimeric PIV. The heterologous antigenic sequences in the first and the second chimeric PIV can be derived from the same virus but encode different proteins, or derived from different viruses. In a preferred embodiment, the heterologous antigenic
25 sequences in the first chimeric PIV are derived from respiratory syncytial virus, and the heterologous antigenic sequences in the second chimeric PIV are derived from human metapneumovirus. In another preferred embodiment, the heterologous antigenic sequences in the first chimeric PIV are derived from respiratory syncytial virus, and the heterologous antigenic sequences in the second chimeric PIV are derived from avian pneumovirus.

30 In certain preferred embodiments, the vaccine formulation of the invention is used to protect against infections caused by a negative strand RNA virus, including but not limited to, influenza virus, parainfluenza virus, respiratory syncytial virus, and mammalian

metapneumovirus (e.g., human metapneumovirus). More specifically, the vaccine formulation of the invention is used to protect against infections by a human metapneumovirus and/or an avian pneumovirus. In certain embodiments, the vaccine 5 formulation of the invention is used to protect against infections by (a) a human metapneumovirus and a respiratory syncytial virus; and/or (b) an avian pneumovirus and a respiratory syncytial virus.

In a preferred embodiment, the invention provides a proteinaceous molecule or metapneumovirus-specific viral protein or functional fragment thereof encoded by a nucleic acid according to the invention. Useful proteinaceous molecules are for example derived from any of the genes or genomic fragments derivable from a virus according to the invention. Particularly useful are the F, SH and/or G protein or antigenic fragments thereof for inclusion as antigen or subunit immunogen, but inactivated whole virus can also be used. Particularly useful are also those proteinaceous substances that are encoded by recombinant 10 nucleic acid fragments that are identified for phylogenetic analyses, of course preferred are those that are within the preferred bounds and metes of ORFs useful in phylogenetic analyses, in particular for eliciting MPV specific antibody or T cell responses, whether in vivo (e.g. for protective purposes or for providing diagnostic antibodies) or in vitro (e.g. by phage display technology or another technique useful for generating synthetic antibodies).

20 A pharmaceutical composition comprising a virus, a nucleic acid, a proteinaceous molecule or fragment thereof, an antigen and/or an antibody according to the invention can for example be used in a method for the treatment or prevention of a MPV infection and/or a respiratory illness comprising providing an individual with a pharmaceutical composition according to the invention. This is most useful when said individual is a human, specifically 25 when said human is below 5 years of age, since such infants and young children are most likely to be infected by a human MPV as provided herein. Generally, in the acute phase patients will suffer from upper respiratory symptoms predisposing for other respiratory and other diseases. Also lower respiratory illnesses may occur, predisposing for more and other serious conditions. The compositions of the invention can be used for the treatment of 30 immuno-compromised individuals including cancer patients, transplant recipients and the elderly.

The invention also provides methods to obtain an antiviral agent useful in the

treatment of respiratory tract illness comprising establishing a cell culture or experimental animal comprising a virus according to the invention, treating said culture or animal with an candidate antiviral agent, and determining the effect of said agent on said virus or its
5 infection of said culture or animal. The invention also provides use of an antiviral agent according to the invention for the preparation of a pharmaceutical composition, in particular for the preparation of a pharmaceutical composition for the treatment of respiratory tract illness, specifically when caused by an MPV infection or related disease, and provides a pharmaceutical composition comprising an antiviral agent according to the invention, useful
10 in a method for the treatment or prevention of an MPV infection or respiratory illness, said method comprising providing an individual with such a pharmaceutical composition.

In certain embodiments of the invention, the vaccine of the invention comprises mammalian metapneumovirus. In certain, more specific embodiments, the mammalian metapneumovirus is a human metapneumovirus. In a preferred embodiment, the mammalian
15 metapneumovirus to be used in a vaccine formulation has an attenuated phenotype. For methods to achieve an attenuated phenotype, see section 5.4.

The invention provides vaccine formulations for the prevention and treatment of infections with PIV, RSV, APV, and/or hMPV. In certain embodiments, the vaccine of the invention comprises recombinant and chimeric viruses of the invention. In certain
20 embodiments, the virus is attenuated.

In a specific embodiment, the vaccine comprises APV and the vaccine is used for the prevention and treatment for hMPV infections in humans. Without being bound by theory, because of the high degree of homology of the F protein of APV with the F protein of hMPV, infection with APV will result in the production of antibodies in the host that will cross-react
25 with hMPV and protect the host from infection with hMPV and related diseases.

In another specific embodiment, the vaccine comprises hMPV and the vaccine is used for the prevention and treatment for APV infection in birds, such as, but not limited to, in turkeys. Without being bound by theory, because of the high degree of homology of the F protein of APV with the F protein of hMPV, infection with hMPV will result in the
30 production of antibodies in the host that will cross-react with APV and protect the host from infection with APV and related diseases.

In certain embodiments, the vaccine formulation of the invention is used to protect

against infections by (a) a human metapneumovirus and a human parainfluenza virus; and/or (b) an avian pneumovirus and a human parainfluenza virus and related diseases.

- In certain embodiments, the vaccine formulation of the invention is used to protect
- 5 against infections by (a) a human metapneumovirus, a respiratory syncytial virus, and a human parainfluenza virus; and/or (b) an avian pneumovirus, a respiratory syncytial virus, and a human parainfluenza virus and related diseases.

- In certain embodiments, the vaccine formulation of the invention is used to protect against infections by a human metapneumovirus, a respiratory syncytial virus, and a human
- 10 parainfluenza virus. In certain other embodiments, the vaccine formulation of the invention is used to protect against infections by an avian pneumovirus, a respiratory syncytial virus, and a human parainfluenza virus, and related diseases.

- Due to the high degree of homology among the F proteins of different viral species, for exemplary amino acid sequence comparisons see Figure 1, the vaccine formulations of
- 15 the invention can be used for protection from viruses different from the one from which the heterologous nucleotide sequence encoding the F protein was derived. In a specific exemplary embodiment, a vaccine formulation contains a virus comprising a heterologous nucleotide sequence derived from an avian pneumovirus type A, and the vaccine formulation is used to protect from infection by avian pneumovirus type A and avian pneumovirus type
- 20 B. In another specific exemplary embodiment, a vaccine formulation contains a virus comprising a heterologous nucleotide sequence derived from an avian pneumovirus subgroup C, and the vaccine formulation is used to protect from infection by avian pneumovirus subgroup C and avian pneumovirus subgroup D.

- The invention encompasses vaccine formulations to be administered to humans and
- 25 animals that are useful to protect against PIV, hMPV, APV (including APV C and APV D), influenza, RSV, Sendai virus, mumps, laryngotracheitis virus, simianvirus 5, human papillomavirus, as well as other viruses, pathogens and related diseases. The invention further encompasses vaccine formulations to be administered to humans and animals that are useful to protect against human metapneumovirus infections, avian pneumovirus infections,
- 30 and related diseases.

In one embodiment, the invention encompasses vaccine formulations that are useful against domestic animal disease causing agents including rabies virus, feline leukemia virus

(FLV) and canine distemper virus. In yet another embodiment, the invention encompasses vaccine formulations that are useful to protect livestock against vesicular stomatitis virus, rabies virus, rinderpest virus, swinepox virus, and further, to protect wild animals against 5 rabies virus.

Attenuated viruses generated by the reverse genetics approach can be used in the vaccine and pharmaceutical formulations described herein. Reverse genetics techniques can also be used to engineer additional mutations to other viral genes important for vaccine production. For example, mutations in the 5' non-coding region may affect mRNA 10 translation, mutations in capsid proteins are believed to influence viral assembly, and temperature-sensitive and cold-adapted mutants are often less pathogenic than the parental virus. (see, e.g., Flint et al., PRINCIPLES OF VIROLOGY, MOLECULAR BIOLOGY, PATHOGENESIS, AND CONTROL, 2000, ASM Press pp 670 - 683, the entire text is incorporated herein by reference). The epitopes of useful vaccine strain variants can be 15 engineered into the attenuated virus. Alternatively, completely foreign epitopes, including antigens derived from other viral or non-viral pathogens can be engineered into the attenuated strain. For example, antigens of non-related viruses such as HIV (gp160, gp120, gp41), parasite antigens (e.g., malaria), bacterial or fungal antigens, or tumor antigens can be engineered into the attenuated strain. Alternatively, epitopes which alter the tropism of the 20 virus *in vivo* can be engineered into the chimeric attenuated viruses of the invention.

Virtually any heterologous gene sequence may be constructed into the chimeric viruses of the invention for use in vaccines. Preferably, moieties and peptides that act as biological response modifiers are constructed into the chimeric viruses of the invention for use in vaccines. Preferably, epitopes that induce a protective immune response to any of a 25 variety of pathogens, or antigens that bind neutralizing antibodies may be expressed by or as part of the chimeric viruses. For example, heterologous gene sequences that can be constructed into the chimeric viruses of the invention include, but are not limited to influenza and parainfluenza hemagglutinin neuraminidase and fusion glycoproteins such as the HN and F genes of human PIV3. In yet another embodiment, heterologous gene sequences that can 30 be engineered into the chimeric viruses include those that encode proteins with immunomodulating activities. Examples of immunomodulating proteins include, but are not limited to, cytokines, interferon type 1, gamma interferon, colony stimulating factors,

interleukin -1, -2, -4, -5, -6, -12, and antagonists of these agents.

In addition, heterologous gene sequences that can be constructed into the chimeric viruses of the invention for use in vaccines include but are not limited to sequences derived from a human immunodeficiency virus (HIV), preferably type 1 or type 2. In a preferred embodiment, an immunogenic HIV-derived peptide that may be the source of an antigen may be constructed into a chimeric PIV that may then be used to elicit a vertebrate immune response. Such HIV-derived peptides may include, but are not limited to, sequences derived from the env gene (*i.e.*, sequences encoding all or part of gp160, gp120, and/or gp41), the pol gene (*i.e.*, sequences encoding all or part of reverse transcriptase, endonuclease, protease, and/or integrase), the gag gene (*i.e.*, sequences encoding all or part of p7, p6, p55, p17/18, p24/25), tat, rev, nef, vif, vpu, vpr, and/or vpx.

Other heterologous sequences may be derived from hepatitis B virus surface antigen (HBsAg); hepatitis A or C virus surface antigens, the glycoproteins of Epstein Barr virus; the glycoproteins of human papillomavirus; the glycoproteins of respiratory syncytial virus, parainfluenza virus, Sendai virus, simianvirus 5 or mumps virus; the glycoproteins of influenza virus; the glycoproteins of herpesviruses; VP1 of poliovirus; antigenic determinants of non-viral pathogens such as bacteria and parasites, to name but a few. In another embodiment, all or portions of immunoglobulin genes may be expressed. For example, variable regions of anti-idiotypic immunoglobulins that mimic such epitopes may be constructed into the chimeric viruses of the invention.

Other heterologous sequences may be derived from tumor antigens, and the resulting chimeric viruses can be used to generate an immune response against the tumor cells leading to tumor regression *in vivo*. These vaccines may be used in combination with other therapeutic regimens, including but not limited to, chemotherapy, radiation therapy, surgery, bone marrow transplantation, etc. for the treatment of tumors. In accordance with the present invention, recombinant viruses may be engineered to express tumor-associated antigens (TAAs), including but not limited to, human tumor antigens recognized by T cells (Robbins and Kawakami, 1996, *Curr. Opin. Immunol.* 8:628-636, incorporated herein by reference in its entirety), melanocyte lineage proteins, including gp100, MART-1/MelanA, TRP-1 (gp75), tyrosinase; Tumor-specific widely shared antigens, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-1, N-acetylglucosaminyltransferase-V, p15; Tumor-specific mutated antigens,

β-catenin, MUM-1, CDK4; Nonmelanoma antigens for breast, ovarian, cervical and pancreatic carcinoma, HER-2/neu, human papillomavirus -E6, -E7, MUC-1.

In even other embodiments, a heterologous nucleotide sequence is derived from a metapneumovirus, such as human metapneumovirus and/or avian pneumovirus. In even other embodiments, the virus of the invention contains two different heterologous nucleotide sequences wherein one is derived from a metapneumovirus, such as human metapneumovirus and/or avian pneumovirus, and the other one is derived from a respiratory syncytial virus. The heterologous nucleotide sequence encodes a F protein or a G protein of the respective virus. In a specific embodiment, a heterologous nucleotide sequences encodes a chimeric F protein, wherein the chimeric F protein contains the ectodomain of a F protein of a metapneumovirus and the transmembrane domain as well as the luminal domain of a F protein of a parainfluenza virus.

Either a live recombinant viral vaccine or an inactivated recombinant viral vaccine can be formulated. A live vaccine may be preferred because multiplication in the host leads to a prolonged stimulus of similar kind and magnitude to that occurring in natural infections, and therefore, confers substantial, long-lasting immunity. Production of such live recombinant virus vaccine formulations may be accomplished using conventional methods involving propagation of the virus in cell culture or in the allantois of the chick embryo followed by purification. Additionally, as bPIV has been demonstrated to be non-pathogenic in humans, this virus is highly suited for use as a live vaccine.

In this regard, the use of genetically engineered PIV (vectors) for vaccine purposes may desire the presence of attenuation characteristics in these strains. The introduction of appropriate mutations (*e.g.*, deletions) into the templates used for transfection may provide the novel viruses with attenuation characteristics. For example, specific missense mutations that are associated with temperature sensitivity or cold adaption can be made into deletion mutations. These mutations should be more stable than the point mutations associated with cold or temperature sensitive mutants and reversion frequencies should be extremely low.

Alternatively, chimeric viruses with "suicide" characteristics may be constructed. Such viruses would go through only one or a few rounds of replication within the host. When used as a vaccine, the recombinant virus would go through limited replication cycle(s) and induce a sufficient level of immune response but it would not go further in the human

host and cause disease. Recombinant viruses lacking one or more of the PIV genes or possessing mutated PIV genes would not be able to undergo successive rounds of replication. Defective viruses can be produced in cell lines which permanently express such a gene(s).

5 Viruses lacking an essential gene(s) would be replicated in these cell lines, however, when administered to the human host, they would not be able to complete a round of replication. Such preparations may transcribe and translate --in this abortive cycle -- a sufficient number of genes to induce an immune response. Alternatively, larger quantities of the strains could be administered, so that these preparations serve as inactivated (killed) virus vaccines. For

10 inactivated vaccines, it is preferred that the heterologous gene product be expressed as a viral component, so that the gene product is associated with the virion. The advantage of such preparations is that they contain native proteins and do not undergo inactivation by treatment with formalin or other agents used in the manufacturing of killed virus vaccines.

15 Alternatively, mutated PIV made from cDNA may be highly attenuated so that it replicates for only a few rounds.

In certain embodiments, the vaccine of the invention comprises an attenuated virus. Without being bound by theory, the attenuated virus can be effective as a vaccine even if the attenuated virus is incapable of causing a cell to generate new infectious viral particles because the viral proteins are inserted in the cytoplasmic membrane of the host thus

20 stimulating an immune response.

In another embodiment of this aspect of the invention, inactivated vaccine formulations may be prepared using conventional techniques to "kill" the chimeric viruses. Inactivated vaccines are "dead" in the sense that their infectivity has been destroyed. Ideally, the infectivity of the virus is destroyed without affecting its immunogenicity. In order to

25 prepare inactivated vaccines, the chimeric virus may be grown in cell culture or in the allantois of the chick embryo, purified by zonal ultracentrifugation, inactivated by formaldehyde or β -propiolactone, and pooled. The resulting vaccine is usually inoculated intramuscularly.

Inactivated viruses may be formulated with a suitable adjuvant in order to enhance the

30 immunological response. Such adjuvants may include but are not limited to mineral gels, e.g., aluminum hydroxide; surface active substances such as lysolecithin, pluronic polyols, polyanions; peptides; oil emulsions; and potentially useful human adjuvants such as BCG,

Corynebacterium parvum, ISCOMS, and virosomes.

Many methods may be used to introduce the vaccine formulations described above, these include but are not limited to oral, intradermal, intramuscular, intraperitoneal, 5 intravenous, subcutaneous, percutaneous, and intranasal and inhalation routes. It may be preferable to introduce the chimeric virus vaccine formulation via the natural route of infection of the pathogen for which the vaccine is designed.

In certain embodiments, the invention relates to immunogenic compositions. The immunogenic compositions comprise a chimeric PIV. In certain embodiments, the 10 immunogenic composition comprises an attenuated chimeric PIV. In certain embodiments, the immunogenic composition further comprises a pharmaceutically acceptable carrier.

Various techniques may be used to evaluate the effectiveness and safeness of a vaccine according to the present invention. An effective vaccine is a vaccine that protects vaccinated individuals from illness due to pathogens, by invoking proper innate, cellular, and 15 humoral responses with minimal side effect. The vaccine must not cause disease. Any techniques that are able to measure the replication of the virus and the immune response of the vaccinated subject may be used to evaluate the vaccine. Non-limiting examples are given in the Example sections, *infra*.

20 **5.6.1. DOSAGE REGIMENS AND ADMINISTRATION OF THE VACCINES
OR IMMUNOGENIC PREPARATIONS OF THE INVENTION**

The present invention provides vaccines and immunogenic preparations comprising chimeric PIV expressing one or more heterologous or non-native antigenic sequences. The vaccines or immunogenic preparations of the invention encompass single or multivalent 25 vaccines, including bivalent and trivalent vaccines. The vaccines or immunogenic formulations of the invention are useful in providing protections against various viral infections. Particularly, the vaccines or immunogenic formulations of the invention provide protection against respiratory tract infections in a host.

A recombinant virus and/or a vaccine or immunogenic formulation of the invention 30 can be administered alone or in combination with other vaccines. Preferably, a vaccine or immunogenic formulation of the invention is administered in combination with other vaccines or immunogenic formulations that provide protection against respiratory tract

diseases, such as but not limited to, respiratory syncytial virus vaccines, influenza vaccines, measles vaccines, mumps vaccines, rubella vaccines, pneumococcal vaccines, rickettsia vaccines, staphylococcus vaccines, whooping cough vaccines or vaccines against respiratory tract cancers. In a preferred embodiment, the virus and/or vaccine of the invention is administered concurrently with pediatric vaccines recommended at the corresponding ages. For example, at two, four or six months of age, the virus and/or vaccine of the invention can be administered concurrently with DtaP (IM), Hib (IM), Polio (IPV or OPV) and Hepatitis B (IM). At twelve or fifteen months of age, the virus and/or vaccine of the invention can be administered concurrently with Hib (IM), Polio (IPV or OPV), MMRII® (SubQ); Varivax® (SubQ), and hepatitis B (IM). The vaccines that can be used with the methods of invention are reviewed in various publications, e.g., The Jordan Report 2000, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, United States, the content of which is incorporated herein by reference in its entirety.

A vaccine or immunogenic formulation of the invention may be administered to a subject *per se* or in the form of a pharmaceutical or therapeutic composition. Pharmaceutical compositions comprising an adjuvant and an immunogenic antigen of the invention (e.g., a virus, a chimeric virus, a mutated virus) may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries which facilitate processing of the immunogenic antigen of the invention into preparations which can be used pharmaceutically. Proper formulation is, or amongst others, dependent upon the route of administration chosen.

When a vaccine or immunogenic composition of the invention comprises adjuvants or is administered together with one or more adjuvants, the adjuvants that can be used include, but are not limited to, mineral salt adjuvants or mineral salt gel adjuvants, particulate adjuvants, microparticulate adjuvants, mucosal adjuvants, and immunostimulatory adjuvants. Examples of adjuvants include, but are not limited to, aluminum hydroxide, aluminum phosphate gel, Freund's Complete Adjuvant, Freund's Incomplete Adjuvant, squalene or squalane oil-in-water adjuvant formulations, biodegradable and biocompatible polyesters,

polymerized liposomes, triterpenoid glycosides or saponins (*e.g.*, QuilA and QS-21, also sold under the trademark STIMULON, ISCOPREP), N-acetyl-muramyl-L-threonyl-D-isoglutamine (Threonyl-MDP, sold under the trademark TERMURTIDE), LPS,

- 5 monophosphoryl Lipid A (3D-MLA sold under the trademark MPL).

The subject to which the vaccine or an immunogenic composition of the invention is administered is preferably a mammal, most preferably a human, but can also be a non-human animal, including but not limited to, primates, cows, horses, sheep, pigs, fowl (*e.g.*, chickens, turkeys), goats, cats, dogs, hamsters, mice and rodents.

- 10 Many methods may be used to introduce the vaccine or the immunogenic composition of the invention, including but not limited to, oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, percutaneous, intranasal and inhalation routes, and via scarification (scratching through the top layers of skin, *e.g.*, using a bifurcated needle).

- 15 For topical administration, the vaccine or immunogenic preparations of the invention may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art.

For administration intranasally or by inhalation, the preparation for use according to the present invention can be conveniently delivered in the form of an aerosol spray.

- 20 presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the
- 25 compound and a suitable powder base such as lactose or starch.

- For injection, the vaccine or immunogenic preparations may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the proteins
- 30 may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

Determination of an effective amount of the vaccine or immunogenic formulation for

administration is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure provided herein.

An effective dose can be estimated initially from *in vitro* assays. For example, a dose
5 can be formulated in animal models to achieve an induction of an immunity response using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to all animal species based on results described herein. Dosage amount and interval may be adjusted individually. For example, when used as an immunogenic composition, a suitable dose is an amount of the composition that when
10 administered as described above, is capable of eliciting an antibody response. When used as a vaccine, the vaccine or immunogenic formulations of the invention may be administered in about 1 to 3 doses for a 1-36 week period. Preferably, 1 or 2 doses are administered, at intervals of about 2 weeks to about 4 months, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual animals. A
15 suitable dose is an amount of the vaccine formulation that, when administered as described above, is capable of raising an immunity response in an immunized animal sufficient to protect the animal from an infection for at least 4 to 12 months. In general, the amount of the antigen present in a dose ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 μ g. Suitable
20 dose range will vary with the route of injection and the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In a specific embodiment, the viruses and/or vaccines of the invention are administered at a starting single dose of at least 10^3 TCID₅₀, at least 10^4 TCID₅₀, at least 10^5 TCID₅₀, at least 10^6 TCID₅₀. In another specific embodiment, the virus and/or vaccines of the
25 invention are administered at multiple doses. In a preferred embodiment, a primary dosing regimen at 2, 4, and 6 months of age and a booster dose at the beginning of the second year of life are used. More preferably, each dose of at least 10^5 TCID₅₀, or at least 10^6 TCID₅₀ is given in a multiple dosing regimen. The replication rate of a virus can be used as an index to adjust the dosage of a vaccine in a clinical trial. For example, assays to test the replication
30 rate of a virus (*e.g.*, a growth curve, *see* Section 5.5. for available assays) can be used to compare the replication rate of the viruses and/or vaccines of the invention to that of the bPIV3, which was demonstrated in previous studies (*see* Clements *et al.*, *J. Clin. Microbiol.*

29:1175-82 (1991); Karron *et al.*, J. Infect. Dis. 171:1107-14 (1995); Karron *et al.*, Ped. Inf. Dis. J. 5:650-654 (1996). These studies showed that a bovine PIV3 vaccine is generally safe and well tolerated by healthy human volunteers, including adults, children 6-60 months of age, and infants 2-6 months of age. In these studies, subjects have received at least a single dose of bPIV3 vaccine from 10^3 TCID₅₀ to 10^6 TCID₅₀. Twelve children received two doses of 10^5 TCID₅₀ PIV3 vaccine instead of one dose without untoward effects.). A comparable replication rate as to bPIV3 suggests that a comparable dosage may be used in a clinical trial. A lower replication rate compared to that of bPIV3 suggests that a higher dosage can be used.

10

5.6.1.1. CHALLENGE STUDIES

This assay is used to determine the ability of the recombinant viruses of the invention and of the vaccines of the invention to prevent lower respiratory tract viral infection in an animal model system, such as, but not limited to, cotton rats or hamsters. The recombinant virus and/or the vaccine can be administered by intravenous (IV) route, by intramuscular (IM) route or by intranasal route (IN). The recombinant virus and/or the vaccine can be administered by any technique well-known to the skilled artisan. This assay is also used to correlate the serum concentration of antibodies with a reduction in lung titer of the virus to which the antibodies bind.

20

On day 0, groups of animals, such as, but not limited to, cotton rats (*Sigmodon hispidus*, average weight 100 g) cynomolgous macaques (average weight 2.0 kg) are administered the recombinant or chimeric virus or the vaccine of interest or BSA by intramuscular injection, by intravenous injection, or by intranasal route. Prior to, concurrently with, or subsequent to administration of the recombinant virus or the vaccine of the invention, the animals are infected with wild type virus wherein the wild type virus is the virus against which the vaccine was generated. In certain embodiments, the animals are infected with the wild type virus at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, 1 week or 1 or more months subsequent to the administration of the recombinant virus and/or the vaccine of the invention.

30

After the infection, cotton rats are sacrificed, and their lung tissue is harvested and pulmonary virus titers are determined by plaque titration. Bovine serum albumin (BSA) 10 mg/kg is used as a negative control. Antibody concentrations in the serum at the time of

challenge are determined using a sandwich ELISA. Similarly, in macaques, virus titers in nasal and lung lavages can be measured.

5

5.6.1.2. TARGET POPULATIONS

In certain embodiments of the invention, the target population for the therapeutic and diagnostic methods of the invention is defined by age. In certain embodiments, the target population for the therapeutic and/or diagnostic methods of the invention is characterized by a disease or disorder in addition to a respiratory tract infection.

10

In a specific embodiment, the target population encompasses young children, below 2 years of age. In a more specific embodiment, the children below the age of 2 years do not suffer from illnesses other than respiratory tract infection.

15

In other embodiments, the target population encompasses patients above 5 years of age. In a more specific embodiment, the patients above the age of 5 years suffer from an additional disease or disorder including cystic fibrosis, leukaemia, and non-Hodgkin lymphoma, or recently received bone marrow or kidney transplantation.

In a specific embodiment of the invention, the target population encompasses subjects in which the hMPV infection is associated with immunosuppression of the hosts. In a specific embodiment, the subject is an immunocompromised individual.

20

In certain embodiments, the target population for the methods of the invention encompasses the elderly.

In a specific embodiment, the subject to be treated with the methods of the invention was infected with hMPV in the winter months.

25

5.6.1.3. CLINICAL TRIALS

Vaccines of the invention or fragments thereof tested in *in vitro* assays and animal models may be further evaluated for safety, tolerance and pharmacokinetics in groups of normal healthy adult volunteers. The volunteers are administered intramuscularly, intravenously or by a pulmonary delivery system a single dose of a recombinant virus of the invention and/or a vaccine of the invention. Each volunteer is monitored at least 24 hours prior to receiving the single dose of the recombinant virus of the invention and/or a vaccine of the invention and each volunteer will be monitored for at least 48 hours after receiving the

dose at a clinical site. Then volunteers are monitored as outpatients on days 3, 7, 14, 21, 28, 35, 42, 49, and 56 postdose.

- Blood samples are collected via an indwelling catheter or direct venipuncture using
- 5 10 ml red-top Vacutainer tubes at the following intervals: (1) prior to administering the dose of the recombinant virus of the invention and/or a vaccine of the invention; (2) during the administration of the dose of the recombinant virus of the invention and/or a vaccine of the invention; (3) 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, and 48 hours after administering the dose of the
- 10 recombinant virus of the invention and/or a vaccine of the invention; and (4) 3 days, 7 days 14 days, 21 days, 28 days, 35 days, 42 days, 49 days, and 56 days after administering the dose of the recombinant virus of the invention and/or a vaccine of the invention. Samples are allowed to clot at room temperature and serum will be collected after centrifugation.

The amount of antibodies generated against the recombinant virus of the invention and/or a vaccine of the invention in the samples from the patients can be quantitated by

15 ELISA. T-cell immunity (cytotoxic and helper responses) in PBMC and lung and nasal lavages can also be monitored.

The concentration of antibody levels in the serum of volunteers are corrected by subtracting the predose serum level (background level) from the serum levels at each

20 collection interval after administration of the dose of recombinant virus of the invention and/or a vaccine of the invention. For each volunteer the pharmacokinetic parameters are computed according to the model-independent approach (Gibaldi *et al.*, eds., 1982, Pharmacokinetics, 2nd edition, Marcel Dekker, New York) from the corrected serum antibody or antibody fragment concentrations.

25

The following examples are illustrative, but not limiting, of the present invention. Cells and Viruses used in the examples are maintained as follows: the RSV A2 strain and the bovine parainfluenza type 3/human parainfluenza type 3 vectored RSV viruses (bPIV3/hPIV3/RSV viruses) were grown in Vero cells in Opti-MEM (Gibco/BRL) in the presence of gentamycin. The modified vaccinia virus Ankara (MVA-T7) or fowl-pox-T7 (FP-T7) which expressed the phage T7 RNA polymerase were grown in chicken embryonic kidney cells (SPAFAS). Vero, HeLa and Hep-2 cells were maintained in MEM (JRH

Biosciences) supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine, non-essential amino acids, and antibiotics.

5 **6. EXAMPLE 1: CONSTRUCTION AND CLONING OF CHIMERIC BOVINE PARAINFLUENZA 3 / HUMAN PARAINFLUENZA 3 cDNA**

In order to substitute the F and HN genes of bPIV3 with those of hPIV3, additional restriction enzyme sites were introduced into the infectious bPIV3 cDNA. Using site-directed mutagenesis, a unique Nhe I site was introduced at nucleotide position 5041 and a Sal I site was introduced at nt 8529 of the bPIV3 cDNA. The modified full-length bPIV3 10 cDNA was treated with Nhe I and Sal I restriction enzymes and a ~14 kb DNA fragment encompassing all of the viral bPIV3 sequences except the F and HN genes, was isolated by gel purification.

To obtain the hPIV3 F and HN gene sequences, a 10 cm dish of confluent Vero cells 15 was infected with a strain of hPIV3 (hPIV3/Tex/12084/1983). After 3 days of incubation at 37°C, the cells were harvested and total RNA was isolated using RNA STAT-LS 50 (Tel-Test Inc.). Viral cDNA was generated by reverse transcription using a hPIV3 specific oligo annealing at position 4828 of the hPIV3 genome. The hPIV3 F and HN genes were 20 amplified by PCR (polymerase chain reaction) using Taq polymerase. The PCR product was cloned into the pT/A TOPO cloning vector (Invitrogen) and from two clones (#11 and #14) the hPIV3 F and HN genes were sequenced. Sequence analysis revealed that for clone #11, the F gene was correct, but the HN gene contained aberrant sequences; for clone #14, the HN 25 gene was correct, but the F gene contained aberrant stop codons. Thus, a plasmid, containing functional hPIV3 F and HN genes, was constructed by combining the correct F gene of #11 with the correct HN gene of #14 in the following manner. Both hPIV3 plasmids (#11 and #14) were digested with NheI and EcoR1. A 1.6 kb fragment harboring the correct F gene 30 was isolated from clone #11 and a 8.5 kb fragment containing the correct HN gene and plasmid sequences, was isolated from clone #14. The two fragments were ligated to produce the intact hPIV3 F and HN genes-containing plasmid. The correct sequence was confirmed by DNA sequence analysis. Finally, a single nucleotide was added at the 3' end of the HN gene in the untranslated region to satisfy the "Rule of Six." The addition of the single nucleotide was accomplished by using the QuikChange mutagenesis kit (Stratagene) and was

confirmed by DNA sequencing. The correct hPIV3 F and HN gene DNA fragment was then isolated by digestion with Nhe 1 and Sal 1 and a 3.5 kb DNA fragment was gel purified.

The full-length b/h PIV3 chimeric cDNA was constructed by ligating the 14.5 kb
5 DNA fragment harboring bPIV3 sequences described above and the 3.5 kb DNA fragment containing the hPIV3 F and HN genes (see Figure 3). The full-length chimeric plasmid DNA was confirmed by extensive restriction enzyme mapping. In addition, the M/F and HN/L gene junctions of the chimeric construct were confirmed by DNA sequencing to both contain bPIV3 and hPIV3 sequences as well as a Nhe 1 and a Sal 1 restriction enzyme site,
10 respectively.

7. EXAMPLE 2: CONSTRUCTION AND CLONING OF CHIMERIC BOVINE PARAINFLUENZA 3/HUMAN PARAINFLUENZA 3 VECTORED RESPIRATORY SYNCYTIAL VIRUS F OR G cDNAs

In order to determine the effects of RSV antigen insertions in position 1 or 2 of the
15 b/h PIV3 genome on virus replication, respiratory syncytial virus (RSV) F and G genes were cloned into different positions of the chimeric bovine parainfluenza 3/human parainfluenza 3 vector (b/h PIV3 vector). See Figure 4.

In order to insert foreign genes into the bovine/human (b/h) PIV3 cDNA, AvrII restriction enzyme sites were introduced in the b/h PIV3 cDNA plasmid (Haller *et al.*, 2000;
20 2001, this is the same construct as in Example 6) by site-directed mutagenesis using the QuickChange kit (Stratagene). One AvrII site was introduced at nucleotide (nt) 104 in the b/h PIV3 genome altering four nucleotides using the following oligo 5'GAA ATC CTA AGA CCC TAG GCA TGT TGA GTC3' and its complement. This restriction enzyme site was used to insert the RSV genes in the first (most 3') position of the viral genome. Another
25 AvrII site was introduced in the N-P intergenic region at nt 1774 changing two nucleotides using the following oligo 5'CCACAACTCAATCAACCTAGGATTGATGGAAAGACAATG 3' and its complement. This restriction site was used to insert the RSV genes in the second position between the N and P genes of b/h PIV3 (Figure 4). Full-length b/h PIV3 cDNAs harboring the AvrII sites at nts 104 and 1774 were tested for functionality by recovering
30 viruses by reverse genetics.

Construction of RSV G cassette (N-P gene stop/start): A DNA fragment was

generated that contained the bPIV3 N-P intergenic region as well as the 3' end sequences of the RSV G gene, using the b/h PIV3 cDNA as PCR template. This fragment was generated by PCR using the following oligos: 5'CCCAACACACCAGGCCAGTAGTCACAA

- 5 AGAGATGACCACTATCAC3' and 5'CCCAAGCTCCTAGGTGAATCTTG
GTTGATTGAGTTGTGG3'. This fragment was then used to carry out overlapping PCR to add the bPIV3 N-P intergenic region to the RSV G gene. For the second PCR reaction, a plasmid containing the RSV G and F gene was used as a DNA template, the oligo 5'CAGCGGATCCTAGGGGAGAAAAGTGTGAGAAAAATGTCC3' and an oligo 10 generated from the short PCR fragment above were used as primers. The resulting PCR fragment containing the RSV G gene linked to the bPIV3 N-P intergenic region and flanking AvrII restriction enzyme sites, was cloned into pGEM3. The RSV G gene was sequenced to confirm the presence of an intact open reading frame and the predicted amino acid sequences. The DNA fragments harboring the RSV G gene were inserted into the first or second position 15 using the AvrII restriction enzyme sites into a subclone harboring only the first 5200 nucleotides of the bPIV3 (1-5 bPIV3) genome that was linearized with AvrII. As used herein and other Examples, 1-5 bPIV3 refers to the nucleotide 1 to 5196 (or 5200) of bovine PIV3 genome. There is a BstB1 site at this location.

- Construction of RSV F cassette (N-P gene start/stop): The RSV F gene fragment was 20 isolated by PCR from a full-length bPIV3/RSV F+G cDNA plasmid using oligos that added AvrII sites at the 5' and 3' end of the RSV F gene, and introduced into the 1-5 bPIV3 plasmid harboring the AvrII site at nt 1774, which was linearized with AvrII. The bPIV3 N-P intergenic region was isolated by PCR using 1-5 bPIV3/RSV G2 as a template. The oligo 5'GACCGTCGACCACAAAGAGATGACCACTATCACC 3' and an oligo annealing in 25 the bPIV3 F gene were used to generate a PCR fragment containing the bPIV3 N-P intergenic region, AvrII site, and bPIV3 sequences up to nt 5200. The PCR fragment was digested with SalI and NheI, and added to the 1-5 bPIV3 plasmid harboring the RSV F gene in position 2, which was treated with SalI and NheI. To introduce the RSV F gene containing the N-P intergenic region into position 1, the 1.8 kb RSV F cassette was excised 30 using AvrII, and ligated into 1-5 bPIV3 containing the AvrII site at nt 104, which was linearized with AvrII.

Construction of the RSV F cassette with a short intergenic region (N stop/N start):

The generation of the RSV F gene with the short N-N intergenic region was accomplished by performing a PCR reaction using 1-5 bPIV3/RSV F2 as a template, the oligo 5'GCGCGTCGACCAAGTAAGAAAAACTTAGGATTAAAGAACCTAGGACTGTA3', 5 and an oligo annealing upstream of the 5' end of the RSV F gene encompassing the AvrII restriction enzyme site. The PCR product containing the RSV F gene and the short N-N intergenic region, was digested with AvrII and introduced into 1-5 bPIV3 nt 104 which was linearized with AvrII.

After confirming proper orientation by restriction enzyme mapping, the plasmids 10 harboring the RSV genes in the first position were digested with SphI and BssHII and 4 kb (1-5 bPIV3/RSV G1) or 4.8 kb (1-5 bPIV3/RSV F1) DNA fragments were isolated. In a second cloning step, the remainder of the b/h PIV3 genome was added as a SphI-BssHII 15.1 kb DNA fragment, yielding full-length cDNAs. The bPIV3 subclones, harboring the RSV genes in the second position, were cut with SphI and NheI, and 5.8 kb (bPIV3/RSV G2) and 15 a 6.5 kb (bPIV3/RSV F2) DNA fragments were isolated. In a second cloning step, the rest of the b/h PIV3 genome was added as an NheI-SphI DNA fragment of 14 kb in size. The full-length chimeric b/h PIV3/RSV plasmids were propagated in STBL-2 cells (Gibco/BRL) that provided high yields of full-length virus cDNA plasmids.

20 **8. EXAMPLE 3: BOVINE PARAINFLUENZA 3/HUMAN
PARAINFLUENZA 3 VECTORED RESPIRATORY SYNCYTIAL
VIRUS F OR G DISPLAYED A POSITIONAL EFFECT WITH
REGARDS TO mRNA PRODUCTION AND PROTEIN EXPRESSION
AS WELL AS VIRUS REPLICATION *IN VITRO***

Three experiments were performed to confirm the effective expression of the RSV F 25 or G gene in the constructs of Example 2, and to determine positional effects of gene insertions in the PIV3 genome.

First, in order to demonstrate RSV protein expression by the chimeric viruses, a Western blot of chimeric virus-infected cell lysates was carried out and probed with RSV-specific antisera. See Figure 5A. Western blots were performed as follows: Chimeric viruses 30 were used to infect (70-80%) subconfluent Vero cells at a MOI of 0.1 or 1.0. Forty-eight hours post infection the media overlay was removed and infected monolayers were washed once with 1 ml of PBS. The cells were subsequently lysed in 400 ml of Laemmli buffer

(Bio-Rad) containing 0.05% b-Mercaptoethanol (Sigma). 15 ml of each sample was separated on 12% Tris-HCl Ready Gel (Bio-Rad) and transferred to nylon membranes using a semi-dry transfer cell (Bio-Rad). Nylon membranes were rinsed in PBS [pH 7.6] 5 containing 0.5% (v/v) Tween-20 (Sigma) (PBST) and blocked with PBST containing 5% (w/v) dry milk (PBST-M) for 20-30 minutes at room temperature. Membranes were incubated with either a mixture of RSV F monoclonal antibodies (WHO 1269, 1200, 1153, 1112, 1243, 1107) at a 1:1000 dilution in PBST-M or RSV G 10181 polyclonal antibody (Orbigen) at a 1:2000 dilution in PBST-M for 1 hour at room temperature. Following four 10 washes with PBST, the membranes were incubated with a secondary horseradish peroxidase-conjugated goat anti-mouse antibody (Dako) at a 1:2000 dilution in PBST-M for 1 hour at room temperature. Membranes were washed 4 times with PBST and developed using a chemiluminescence substrate (Amersham Pharmacia) and exposed to Biomax Light Film (Kodak) for visualization of protein bands.

15 Consistent with the reduced replication efficiency of b/h/RSV F1*N-N in Vero cells (Figure 5C, *see below*), the amount of RSV F₁ detected at 48 hours post infection was about 10 times less than that present in b/h PIV3/RSV F2 or wild-type RSV A2 infected cells (compare lanes 2, 3, and 4, Figure 5A). A 50 kDa band representing the F₁ fragment was detected in cells infected with all chimeric viruses as well as wild-type RSV. However, there 20 was greater accumulation of a 20 kDa F fragment in infected cell lysates of chimeric viruses compared to wild-type RSV. When b/h PIV3/RSV F1*N-N infections were repeated at a higher MOI of 1.0 (Figure 5A, lane 1), the F₁ fragment in b/h PIV3/RSV F1 infected cells accumulated to wild-type RSV levels at 48 hours post-infection. The relative amount of the 50 kDa and 20 kDa F₁ fragments in b/h PIV3/RSV F1 or b/h PIV3/RSV F2 infected cells was 25 approximately 1:5. No F₀ was detected in cells infected with chimeric viruses indicating that the F₀ precursors were efficiently processed during b/h PIV3/RSV F1 and b/h PIV3/RSV F2 infections as was also observed in wild-type RSV infections.

The relative expression of RSV G in b/h PIV3/RSV G1, b/h PIV3/RSV G2 and wild-type RSV infected cells is shown in Figure 5A. Both the immature and glycosylated forms of 30 RSV G that migrated at approximately 50 kDa and 90 kDa, respectively, were detected. b/h PIV3/RSV G1 infected cells showed levels of RSV G expression similar to that seen in wild-type RSV infected cells (lanes 1 and 3, Figure 5A). However, in b/h PIV3/RSV G2 infected

cells, the accumulation of RSV G was about 2-3 times more than that present in wild-type RSV infected cells (lanes 2 and 3, Figure 5A). Collectively, these data showed that the chimeric b/h PIV3/RSV efficiently expressed the RSV proteins in either position 1 or 2.

- 5 However, the viruses harboring the RSV genes in position 2 expressed higher levels of RSV proteins.

Next, Northern blot analysis showed that the mRNA transcription correlated with the result of the protein expression demonstrated by the Western blot, *see* Figure 5B. Northern blot was performed as follows: total cellular RNA was prepared from virus-infected cells
10 using Trizol LS (Life Technologies). The RNA was further purified by one phenol-chloroform extraction and precipitated with ethanol. RNA pellets were resuspended in diethyl pyrocarbonate-treated water and stored at -80°C. Equal amounts of total RNA were separated on 1% agarose gels containing 1% formaldehyde and transferred to nylon membranes (Amersham Pharmacia Biotech) using a TurboBlotter apparatus (Schleicher & Schuell). The blots were hybridized with digoxigenin (DIG)-UTP-labeled riboprobes
15 synthesized by in vitro transcription using a DIG RNA labeling kit (Roche Molecular Biochemicals). Hybridization was carried out at 68°C for 12 h in Express Hyb solution (Clontech). The blots were washed at 68°C twice with 2X SSC (1X SSC contained 0.015 M NaCl with 0.015 M sodium citrate)-0.1% sodium dodecyl sulfate (SDS) followed by one
20 wash with 0.5X SSC-0.1% SDS and a final wash with 0.1X SSC-0.1% SDS. Signals from the hybridized probes were detected by using a DIG-Luminescent detection kit (Roche Molecular Biochemicals) and visualized by exposure to BioMax ML film (Kodak).

Northern analysis of b/h PIV3/RSV F1*N-N, b/h PIV3/RSV F2, b/h PIV3/RSV G1 and b/h PIV3/RSV G2 showed that the viral mRNA levels for RSV F or RSV G correlated
25 well with the RSV protein levels observed (Figure 5B). The lowest levels of RSV F mRNAs were observed for b/h PIV3/RSV F1*N-N which also displayed the least amount of RSV F protein produced. b/h PIV3/RSV G1 produced less RSV G mRNAs resulting in lower RSV G protein levels than was observed for b/h PIV3/RSV G2.

Finally, growth of different virus (with RSV F or G gene at either position 1 or
30 position 2) correlates with the results of the protein expression and the RNA transcription. The growth curve showed in Figure 5C was obtained as follows: Vero cells were grown to 90% confluence and infected at an MOI of 0.01 or 0.1 with b/h PIV3, b/h PIV3 RSV F1, b/h

PIV3 RSV G1, b/h PIV3 RSV F2, and b/h PIV3 RSV G2. The infected monolayers were incubated at 37°C. At 0, 24, 48, 72, 96 and 120 hours post-infection, cells and media were harvested together and stored at -70°C. Virus titers for each time point harvest were 5 determined by TCID₅₀ or plaque assays in Vero cells. TCID₅₀ assays were inspected visually for CPE following incubation at 37°C for 6 days, while plaque assays were immunostained with RSV polyclonal antisera for quantification after 5 days of incubation.

At an MOI of 0.01 in Vero cells, the chimeric viruses harboring the RSV G or F genes in the first position (b/h PIV3 RSV G1 and b/h PIV3 RSV F1*N-N) replicated at a 10 slower rate, yielded lower peak titers, and exhibited a greater lag phase than the viruses that contained the RSV genes in the second position. Peak titers of b/h PIV3/RSV F1*N-N and b/h PIV3/RSV G1 at 96 hours post-infection were 10^{6.7} and 10^{5.5} TCID₅₀/ml, respectively (Figure 5C). In contrast, peak titers of b/h PIV3/RSV F2 and b/h PIV3/RSV G2 were 10^{8.0} and 10^{7.4} at 72 and 96 hours post-infection, respectively (Figure 5C). The b/h PIV3 control 15 virus displayed peak titers of 10^{8.0} TCID₅₀/ml, respectively (Figure 5C). The b/h PIV3/RSV F2 yielded 1.3 log₁₀ higher titers than b/h PIV3/RSV F1*N-N. The b/h PIV3/RSV G2 replicated to 1.9 log₁₀ higher titers than b/h PIV3/RSV G1. The results indicated that the chimeric viruses harboring the RSV genes in the first position were delayed in onset for replication *in vitro* compared to chimeric viruses containing the RSV genes in the second 20 position.

To determine whether higher titers of b/h PIV3/RSV F1*N-N and b/h PIV3/RSV G1 could be achieved at all, the growth curves were repeated at a higher MOI of 0.1. At an MOI of 0.1, the peak titers of b/h PIV3/RSV F1*N-N and b/h PIV3/RSV G1 increased by 0.5 to 1.3 log₁₀ (data not shown). The lag phases of these viruses were reduced and peak titers were 25 achieved earlier during the growth cycle.

9. EXAMPLE 4: POSITIONAL EFFECT OF eGFP INSERTIONS IN THE BOVINE PARAINFLUENZA 3/HUMAN PARAINFLUENZA 3 GENOME ON VIRUS REPLICATION

The effect of gene insertions into the bovine/human PIV3 vector backbone was assessed systematically by introducing the eGFP gene sequentially between all genes of PIV3 30 and observing the effect on virus replication and eGFP expression (Figure 6). This type of assay investigates the importance of the transcriptional gradient observed for

paramyxoviruses that yields specific ratios of viral mRNAs. Insertion of foreign genes will perturb these ratios and result in the synthesis of different amounts of viral proteins which may influence virus replication. The eGFP gene was chosen for this assay since it will not be
5 incorporated into the virion membrane, and therefore should not interfere with viral processes such as packaging, budding, entry, etc. The eGFP gene was inserted into four positions of the b/h PIV3 genome, three of which were characterized for eGFP expression and virus replication. The eGFP gene cassette was linked to the bPIV3 N-P intergenic region. b/h GFP1 harbored the eGFP gene cassette in the 3' most proximal position of the
10 b/h PIV3 genome. b/h PIV3/GFP2 contained the eGFP gene cassette between the N and P genes of the b/h PIV3 genome. b/h PIV3/GFP3 was located between P and M, and b/h PIV3/GFP4 had the eGFP gene between M and F of b/h PIV3 (Figure 6).

Construction of the eGFP gene cassette: the template of the eGFP gene is commercially available, e.g., it can be purchased from BD Biosciences (pIRES2-EGFP) or
15 Clontech (pEGFP-N1). See Hoffmann *et al.*, Virology 267:310-317 (2000). The eGFP gene was isolated by PCR and the bPIV3 N-P intergenic region was added by employing the overlapping PCR method, using the following oligos: 5'ATTCCTAGGATGGTGAGCAAG GGCG3', 5'GGACGAGCTGTACAAGTAAAAAAATAGCACCTAATCATG3', and 5'CTACCTAGGTGAATCTTGGTTG3'. The eGFP cassette was inserted into pCR2.1,
20 sequenced, and adherence to the rule-of-six was confirmed. Then the eGFP cassette was digested with AvrII, gel purified, and inserted into positions 1, 2, 3, and 4 of b/h PIV3 as described below.

Generation of full-length cDNAs harboring the eGFP gene in positions 1 and 2: the eGFP gene cassette was inserted into the 1-5 bPIV3 plasmids which contained bPIV3
25 sequences from nts 1 – 5200 and an AvrII restriction enzyme site either at nt 104 (position 1) or nt 1774 (position 2). After confirming proper orientation by restriction enzyme mapping, the plasmid harboring the eGFP gene in the first position was digested with SphI and BssHII and 4 kb (1-5 eGFP1) DNA fragments were isolated. Next, the rest of the b/h PIV3 genome was added as a SphI-BssHII 15.1 kb DNA fragment, yielding full-length cDNAs. For
30 generation of full-length cDNA comprising the eGFP in position 2, the bPIV3 subclones harboring the eGFP genes in the second position were cut with SphI and NheI, and 5.8 kb (1-5 eGFP2) DNA fragments were isolated. Next, the rest of the b/h PIV3 genome was added

as an NheI-SphI DNA fragment of 14 kb in size. The full-length chimeric b/h PIV3/eGFP plasmids were propagated in STBL-2 cells (Gibco/BRL) that provided high yields of full-length virus cDNA plasmids.

- 5 Generation of full-length cDNAs harboring the eGFP gene in positions 3 and 4: in order to insert the eGFP cassette into position 3 of the b/h PIV3 genome, an AvrII restriction enzyme site was introduced at nt 3730 in the P-M intergenic region of a subclone containing nts 1 – 5200 of bPIV3, altering two nucleotides. The following oligo and its complement were used in a QuickChange PCR reaction to introduce the AvrII site:
- 10 5'GGACTAATCAATCCTAGGAAACAATGAGCATCAC3'. The eGFP cassette was digested with AvrII and ligated into the AvrII linearized 1-5 bPIV3 subclone harboring the AvrII site at nt 3730. A 5.5 kb DNA fragment from SphI to NheI was isolated from the GFP containing subclone and introduced into the b/h PIV3 cDNA digested with SphI and NheI to produce a full-length plasmid. In order to add the eGFP gene cassette into position 4 of the
- 15 b/h PIV3 genome, a subclone containing b/h PIV3 sequences from nts 1- 8500 was generated. This subclone was linearized with NheI (nt 5042), and the eGFP cassette containing compatible AvrII ends was inserted. Then the subclone harboring the eGFP cassette was digested with SphI and XhoI and a 7.1 kb DNA fragment was isolated. The b/h PIV3 plasmid was treated with SphI and XhoI and a 11 kb fragment was produced. These
- 20 two DNA fragments were ligated to generate b/h PIV3/GFP4.

- The amount of eGFP produced by b/h PIV3/GFP1, 2, and 3 was assessed in two ways. First, the amount of green cells produced upon infecting Vero cells with b/h PIV3 GFP1, 2, and 3 at MOIs of 0.1 and 0.01 for 20 hours, was determined using a fluorescent microscope (Figure 7A). b/h PIV3/GFP3 produced strikingly fewer green cells than b/h
- 25 PIV3/GFP1 or 2.

- Secondly, western analysis was performed on infected cells and the blots were probed with a GFP MAb as well as a PIV3 PAb. The initial observation that b/h PIV3/GFP3 produced dramatically less eGFP protein, was confirmed (Figure 7B). b/h PIV3 GFP1 and GFP2 produced similar amounts of eGFP protein. The western blots methods controlled for
- 30 same volume loading by probing with a PIV3 antibody (Figure 7B). Interestingly, all three viruses showed similar amounts of PIV3 proteins (the HN protein is the most prominent band) produced. These results suggested that b/h PIV3/GFP3 transcribed less GFP mRNAs

in position 3 as compared to positions 1 and 2. This data confirmed the presence of a transcriptional gradient of viral mRNAs in paramyxoviruses. The level of production of the PIV3 HN protein was not affected by the eGFP gene insertions (Figure 7B).

5 In order to determine whether the GFP gene insertions had an effect on the kinetics of virus replication of b/h PIV3/GFP1, 2, and 3, multicycle growth curves in Vero cells were carried out (Figure 7C). The growth curves showed that b/h PIV3/GFP1 had a delayed onset of virus replication at 24 and 48 hours post-infection than b/h PIV3/GFP2 or GFP3. However, the final peak titers obtained were similar for all three viruses. The kinetics of 10 replication for b/h PIV3/GFP2 and GFP3 were nearly identical (Figure 7C). Interestingly, the altered ratios of viral mRNAs did not appear to effect virus replication significantly.

10. EXAMPLE 5: CONSTRUCTION AND CLONING OF CHIMERIC BOVINE PARAINFLUENZA 3/HUMAN PARAINFLUENZA 3 VECTORED RESPIRATORY SYNCYTIAL VIRUS F WITH DIFFERENT INTERGENIC REGIONS

15 Three different constructs were used to determine the effect of intergenic region (nucleotides between each mRNA, *e.g.*, nucleotides between the F gene and the N gene) on protein expression and viral replication. *See* Figure 8. The first construct was b/h PIV3 vectored RSV F1* N-N in position 1, which had a shorter bPIV N gene stop/N gene start sequence (RSV F1* N-N in Figure 4); the second construct was b/h PIV3 vectored RSV F at 20 position 1 (RSV F2 in Figure 4); and the last one was b/h PIV3 vectored RSV at position 1 (RSV F1 in Figure 4). All three constructs were generated according to the cloning strategies described in section 7, Example 2.

The most dramatic difference between the two cassettes is the distance between the N gene start sequence and the N translation start codon in b/h PIV3/RSV F1*N-N which was 25 only 10 nts long. In contrast, this distance is 86 nts long in b/h PIV3/RSV F2. The other difference is the use of the N gene start sequence in b/h PIV3/RSV F1*N-N rather than the P gene start sequence as was done in b/h PIV3/RSV F2. In order to determine whether the distance between the transcription gene start and the translation start of a viral transcription unit has an effect on virus replication, the b/h PIV3/RSV F1 construct was generated that 30 contained the identical RSV F gene cassette as was used for b/h PIV3/RSV F2.

**11. EXAMPLE 6: THE LENGTH AND/OR NATURE OF THE
INTERGENIC REGION DOWNSTREAM OF THE RESPIRATORY
SYNCYTIAL VIRUS GENE HAS AN EFFECT ON VIRUS
REPLICATION**

5 The three constructs in Example 5 were used in the following experiments to determine the effects of the intergenic region on viral protein expression and viral replication. See Figure 9.

First, RSV F protein expression for b/h PIV3/RSV F1, b/h PIV3/RSV F1*N-N, and b/h PIV3/RSV F2 was compared at 24 and 48 hrs post-infection at an MOI of 0.1 in Vero 10 cells using Western blots. Western blots were performed as follows: Chimeric viruses were used to infect (70-80%) subconfluent Vero cells at a MOI of 0.1. Twenty-four hours and forty-eight hours post infection the media overlay was removed and infected monolayers were washed once with 1 ml of PBS. The cells were subsequently lysed in 400 ml of Laemmli buffer (Bio-Rad) containing 0.05% b-Mercaptoethanol (Sigma). 15 ml of each 15 sample was separated on 12% Tris-HCl Ready Gel (Bio-Rad) and transferred to nylon membranes using a semi-dry transfer cell (Bio-Rad). Nylon membranes were rinsed in PBS (pH 7.6) containing 0.5% (v/v) Tween-20 (Sigma) (PBST) and blocked with PBST containing 5% (w/v) dry milk (PBST-M) for 20-30 minutes at room temperature. Membranes were incubated with either a mixture of RSV F monoclonal antibodies (WHO 20 1269, 1200, 1153, 1112, 1243, 1107) at a 1:1000 dilution in PBST-M in PBST-M for 1 hour at room temperature. Following 4 washes with PBST, the membranes were incubated with a secondary horseradish peroxidase-conjugated goat anti-mouse antibody (Dako) at a 1:2000 dilution in PBST-M for 1 hour at room temperature. Membranes were washed 4 times with PBST and developed using a chemiluminescence substrate (Amersham Pharmacia) and 25 exposed to Biomax Light Film (Kodak) for visualization of protein bands.

b/h PIV3/RSV F1 expressed RSV F₁ protein levels at 24 and 48 hrs post-infection close to the levels observed for b/h PIV3/RSV F2 but much higher than those of b/h PIV3/RSV F1*N-N. Therefore, the spacing between the gene start element and the translation start codon may be critical for virus replication. The N gene start sequences were 30 changed to P gene start sequences, however this change only incurred the alteration of a single nucleotide. Either of these factors may be responsible for rescuing the RSV F protein

expression phenotype.

Next, multicycle growth curves were carried out to compare the kinetics of virus replication of b/h PIV3/RSV F1, b/h PIV3/RSV F1*N-N, and b/h PIV3/RSV F2 in Vero cells at an MOI of 0.1 (see Figure 9B), which was performed as follows: Vero cells were grown to 5 90% confluence and infected at an MOI of 0.1 with b/h PIV3, b/h PIV3/RSV F1*N-N, b/h PIV3/RSV F1, and b/h PIV3/RSV F2. The infected monolayers were incubated at 37°C. At 0, 24, 48, 72, and 96 hours post-infection, cells and media were harvested together and stored at -70°C. Virus titers for each time point harvest were determined by plaque assays in Vero 10 cells. The plaque assays were immunostained with RSV polyclonal antisera for quantification after 5 days of incubation.

As was shown on Figure 9B, the onset of replication of b/h PIV3/RSV F1*N-N was delayed and peak titers were lower than those of b/h PIV3/RSV F2. In contrast, b/h PIV3/RSV F1 displayed a growth curve that was nearly identical to that observed for b/h 15 PIV3/RSV F2.

12. EXAMPLE 7: CLONING OF TRIVALENT BOVINE PARAINFLUENZA 3/HUMAN PARAINFLUENZA 3 VECTORED CONSTRUCTS

The following examples relate to the generation of trivalent vaccines that harbor the 20 surface glycoproteins (F and HN) of hPIV3, RSV F, and hMPV F to protect children from disease caused by RSV, hMPV and hPIV3 using a single live attenuated virus vaccine. These trivalent viruses were recovered by reverse genetics.

The construction of two virus genomes, each comprising a chimeric b/h PIV3 backbone with two additional heterologous sequence insertions, wherein one heterologous 25 nucleotide sequence is derived from a metapneumovirus F gene and another heterologous nucleotide sequence is derived from a respiratory syncytial virus F gene, were done as follows (see Figure 10): plasmids b/h PIV3/RSV F2 or b/h PIV3/hMPV F2 was digested with SphI and NheI, and a 6.5 kb fragment was isolated. The full-length cDNA for b/h PIV3 RSV F1 or b/h PIV3/hMPV F1 was digested with SphI and NheI and a 14.8 kb DNA fragment was 30 isolated and ligated with the 6.5 kb DNA fragment derived from plasmid b/h PIV3/RSV F2 or b/h PIV3/hMPV F2 to generate full-length viral cDNAs.

Virus with the above described constructs has been amplified in Vero cells. The engineered virus as described herein can be used as a trivalent vaccine against the parainfluenza virus infection, metapneumovirus infection, and the respiratory syncytial virus
5 infection.

13. EXAMPLE 8: CLONING OF TWO RESPIRATORY SYNCYTIAL VIRUS F TO THE BOVINE PARAINFLUENZA 3/HUMAN PARAINFLUENZA 3 VECTOR

Chimeric viruses that carry two copies of the RSV F gene were designed in order to
10 determine whether more RSV protein produced by the chimeric virus will result in an improved immunogenicity. This virus was rescued by reverse genetics, biologically cloned and amplified in Vero cells to yield a virus stock with a titer of 1×10^6 pfu/ml. This virus, b/h PIV3/RSV F1F2, can be used to assess for virus growth kinetics, for RSV F protein production, and for replication and immunogenicity in hamsters.

15 The constructs were generated in the following manner (see Figure 11): the 1-5 RSV F2 plasmid was digested with SphI and NheI, and a 6.5 kb fragment was isolated. The full-length cDNA for b/h PIV3 RSV F1 was digested with SphI and NheI and a 14.8 kb DNA fragment was isolated and ligated with the 6.5 kb DNA fragment derived from 1-5 bPIV3/RSV F2 to generate full-length viral cDNAs.

20

14. EXAMPLE 9: CONSTRUCTION AND CLONING OF BOVINE PARAINFLUENZA 3/HUMAN PARAINFLUENZA 3 VECTORED HUMAN METAPNEUMOVIRUS F cDNA

The F gene of human metapneumovirus (hMPV) was inserted in positions 1 and 2 of the b/h PIV3 genome (Figure 12). The hMPV F gene cassette harbored the bPIV3 N-P
25 intergenic region. The hMPV F gene plasmid (pRF515) was used, and a single nucleotide mutation in the hMPV F gene was corrected (*i.e.*, nucleotide 3352 was corrected from C to T (wild type)), generating pRF515-M4. The bPIV3 N-P intergenic region was added at the 3' end of the hMPV F gene using overlapping PCR. For hMPV F, the overlapping PCR oligo was 5'GGCTTCATACCACTATAATTAGAAAAATAGCA

30 CCTAATCATGTTCTTACAATGGTCGACC 3'. During this cloning step, oligos were used at the 5' end (5' GCAGCCTAGGCCGCAATAACAATGTCTGGAAAGTGGTG ATC 3')

and at the 3' end of the hMPV F gene cassette (5' CTACCTAGGTGAATCTT TGGT TG 3') in the PCR reaction that contained AvrII restriction enzyme sites. The hMPV F gene cassette was adjusted to conform to the rule of six using QuickChange mutagenesis kit and the 5 following oligos (5'CCTAGGCCGCAATAGACAATGT CTTGG 3', 5'CCAAGACATT GTCTATTGCGGCCTAGG 3'). Full-length b/h PIV3/hMPV F1 (position 1) and F2 (position 2) cDNA plasmids were generated in the same fashion as described in section 9, Example 4, *supra*, for b/h PIV3/eGFP1 and eGFP2.

10 **15. EXAMPLE 10: IMMUNOPRECIPITATION AND REPLICATION
ASSAYS OF BOVINE PARAINFLUENZA 3/HUMAN
PARAINFLUENZA 3 VECTORED HUMAN METAPNEUMOVIRUS F**

To confirm that the F protein was expressed in the b/h PIV3 vectored human metapneumovirus F at position 2 (hMPV F2), guinea pig or human antiserum were used to immunoprecipitate the hMPV F protein (see Figure 13A). For immunoprecipitation of the 15 hMPV F protein expressed by b/h PIV3, Vero cells were infected with b/h PIV3 or b/h PIV3/hMPV F2 at an MOI of 0.1 or 0.05. Twenty-four hours post-infection, the cells were washed once with DME without cysteine and minus methionine (ICN) and incubated in the same media for 30 min. The media was removed and 0.5 ml DME lacking cysteine and methionine containing 100 µCi of [³⁵S]-Pro-Mix (Amersham) was added to the cells. The 20 infected cells were incubated in the presence of ³⁵S-isotopes for 5 hours at 37°C. Media was removed and the infected cells were lysed in 0.3 M RIPA buffer containing protease inhibitors. The cell lysate was incubated with hMPV guinea pig or human polyclonal antisera and bound to IgG-agarose (Sigma). After washing three times with 0.5 M RIPA buffer, the samples were fractionated on a 10% protein gel. The gel was dried and exposed 25 to X-ray film.

The expression of hMPV F protein by b/h PIV3/hMPV F2 was shown by immunoprecipitation using the gp and human anti-hMPV antisera (Figure 13A). Interestingly, a specific band migrating at approximately 80 kDa was observed in the lysates of b/h PIV3/hMPV F2. This size corresponded to the F precursor protein, F₀. Non-specific 30 bands of different sizes were also observed in the b/h PIV3 and mock control lanes (Figure 13). This data suggested that the b/h PIV3/hMPV F2 expressed the hMPV F protein.

However, the hMPV antibody reagents available are limited and these antisera interact only with the precursor of the hMPV F protein. It could also be possible that the cleaved F1 is unstable and thus not easily visualized using this method.

5 Growth curves were performed to determine the kinetics of virus replication of b/h PIV3/hMPV F2 and compare them to those observed for b/h PIV3 and b/h PIV3/RSV F2 in Vero cells at an MOI of 0.1 (Figure 13B). The data showed that b/h PIV3/hMPV F2 displayed a delayed onset of replication at 24 hours post-infection compared to b/h PIV3/RSV F2. However, at 48 hours post-infection and beyond, a difference in replication
10 was no longer observed.

Growth curves were also performed to determine the kinetics of viral replication of b/h PIV3/hMPV F1 and compare them to those observed for b/h PIV3/hMPV F2 and b/h PIV3 in Vero cells at an MOI of 0.01 (Figure 13C). The data showed that b/h PIV3/hMPV F1 had a delayed onset of replication and yields lower peak titers compared to b/h PIV3/hMPV
15 F2 or b/h PIV3. The plaque size of b/h hMPV F1 is also smaller compared to b/h hMPV F2.

The chimeric viruses, b/h PIV3/hMPV F1 and F2 were also assessed for their ability to infect and replicate in Syrian Golden hamsters (Table 5). The results showed that b/h PIV3/hMPV F1 and F2 replicated in the nasal turbinates and lungs of hamsters to levels observed for b/h PIV3. Even hMPV replicated to titers of 5.3 and 3.6 log₁₀ TCID₅₀/g tissue
20 in the upper and lower respiratory tracts of hamsters. These data showed that b/h PIV3/hMPV F1 and F2 could efficiently infect and replicate in the respiratory tract of hamsters, demonstrating thereby that hamsters represent a suitable small animal model to determine immunogenicity of hMPV as well as utilize this animal model to evaluate hMPV vaccine candidates.

25

30

Table 5

**Replication of b/h PIV3 Expressing
the hMPV F Protein in Positions 1 or 2 in Hamsters**

	Virus ^a	Mean virus titer on day 4 post-infection	
		(log ₁₀ TCID ₅₀ /g tissue ± S.E.) ^b	Lungs
		Nasal turbinates	Lungs
5	b/h PIV3	4.8 ± 0.2	5.6 ± 0.6
	b/h hMPV F1	5.3 ± 0.5	5.7 ± 0.4
10	b/h hMPV F2	5.7 ± 0.5	4.6 ± 0.3
	hMPV	5.3 ± 0.1	3.6 ± 0.3

^a Groups of six hamster were inoculated intranasally with 1x 10⁶ pfu of indicated virus.

^b Standard error

Note: TCID₅₀ assays were read for CPE on Day 10.

**16. EXAMPLE 11: CLONING OF THE SOLUBLE RESPIRATORY
SYNCYTIAL VIRUS F GENE CONSTRUCT**

A construct containing a single copy of the soluble RSV F gene, a version of the RSV F gene lacking the transmembrane and cytosolic domains, was also generated (Figure 14).

This construct can be used to test for immunogenicity. Its advantage would be the inability of the soluble RSV F to be incorporated into the virion membrane. Therefore this virus may be viewed as a safer chimeric virus since its virus tropism is not expected to change. The cDNA plasmid for b/h PIV3/sol RSV F can be rescued by reverse genetics.

The plasmid 1-5/RSV F2 (described previously) was used as a DNA template for PCR. The oligo RSV f.2 (5'GCTGTAACAGAATTGCAGTC 3') (which anneals at nt 5946 of RSV) and the oligo 5'CGTGGTCGACCATTGTAAGAACATGATTAGGTGCTAT TTTTATTTAATTGTGGTGGATTACCGGC3' were employed to remove the transmembrane and cytoplasmic domains of RSV F, deleting 150 nucleotides. The resulting PCR fragment was digested with HpaI and SalI and introduced into 1-5 RSV F2 treated with HpaI and SalI to yield 1-5 bPIV3/sol RSV F. This plasmid was digested with SphI and NheI and the resulting fragment was introduced into a b/h PIV3 cDNA digested with SphI and NheI to generate a full-length cDNA.

17. EXAMPLE 12: EXPRESSION OF HUMAN METAPNEUMOVIRUS F IN CELLS INFECTED WITH BOVINE PARAINFLUENZA 3/HUMAN PARAINFLUENZA 3 VECTORED HUMAN METAPNEUMOVIRUS F

5 The b/h 104 hMPV F virus stocks were serially diluted 10 fold and used to infect subconfluent Vero cells. Infected cells were overlayed with optiMEM media containing gentamycin and incubated at 35°C for 5 days. Cells were fixed with 100% methanol and immunostained with 1:1000 dilution of anti-hMPV001 guinea pig sera followed by 1:1000 dilution of anti-guinea pig HRP conjugated antibodies. Expression of hMPV F is visualized
10 by specific color development in the presence of the AEC substrate system (DAKO corporation). *See Figure 15A.*

 The b/h NP-P hMPV F virus stocks were serially diluted 10 fold and used to infect subconfluent Vero cells. Infected cells were overlayed with 1% methyl cellulose in EMEM/L-15 medium (JRH Biosciences; Lenexa, KS) supplemented with 1x L15/MEM
15 media containing penicillin/streptomycin, L-glutamine and fetal bovine serum. Infected cells were incubated at 35°C for 5 days, fixed with 100% methanol and immunostained with 1:1000 dilution of anti-hMPV001 guinea pig sera followed by 1:1000 dilution of anti-guinea pig HRP conjugated antibodies. (*See Figure 15B.*) The anti hMPV001 guinea pig serum is specific for hMPV001 proteins and do not bind to b/h PIV3 proteins.

20

18. EXAMPLE 13: RESCUE OF CHIMERIC BOVINE PARAINFLUENZA TYPE 3 / HUMAN PARAINFLUENZA TYPE 3 VIRUS IN HE LA CELLS AND VERO CELLS

 Rescue of the chimeric b/h PIV3 virus was done using a similar procedure as for bPIV3 rescue. Rescue of b/h PIV3 chimeric virus by reverse genetics was carried out in
25 HeLa cells using LipofectACE (Gibco/BRL). The 80% confluent HeLa cells, Hep-2 cells, or Vero cells were infected with MVA at an MOI of 4. One hour post-infection, the full-length anti-genomic b/h PIV3 cDNA (4 µg) was transfected into the infected HeLa or Vero cells together with the NP (0.4 µg), P (0.4 µg), and L/pCITE (0.2 µg) expression plasmids.
 Forty hours post-transfection, the cells and the cell supernatant were harvested (P0) and
30 subjected to a single freeze-thaw cycle. The resulting cell lysate was then used to infect a fresh Vero cell monolayer in the presence of 1-beta-D-arabinofuranosylcytosine (ara C), a

- replication inhibitor of vaccinia virus, to generate a P1 virus stock. The supernatant and cells from these plates were harvested, freeze-thawed once and the presence of bPIV3 virus particles was assayed for by immunostaining of virus plaques using PIV3-specific antiserum.
- 5 The cell lysates of the P1 harvest resulted in complete CPE of the Vero cell monolayers and immunostaining indicated the presence of an extensive virus infection.

19. EXAMPLE 14: RESCUE OF BOVINE PARAINFLUENZA TYPE 3/HUMAN PARAINFLUENZA TYPE 3 VECTORED HUMAN METAPNEUMOVIRUS F VIRUSES

- 10 The b/h PIV3 viruses expressing hMPV F at position one (b/h 104 hMPV F) or position two (b/h NP-P hMPV F) were obtained as follows. HEp-2 or Vero cells at 80-90% confluence in 6 well dishes were infected with Fowlpox-T7 at a multiplicity of infection (m.o.i) of 0.1 to 0.3. Following infection with Fowlpox-T7, cells were washed once with PBS and transfected with the following amounts of plasmid DNA: full length b/h 104 hMPV
- 15 F or b/h NP-P hMPV F cDNA 2.0 µg, pCite N 0.4 µg, pCite P 0.4 µg, pCite L 0.2 µg. (The pCite plasmids have a T7 promoter followed by the IRES element derived from the encephalomyocarditis virus (EMCV)). Transfection was performed in the presence of Lipofectamine 2000 (Invitrogen) according to manufacturer's instruction. The transfection reaction was incubated at 33°C for 5 to 12 hours following which the media containing
- 20 lipofectamine 2000 was replaced with 2 ml of fresh OptiMEM containing gentamicin. The transfected cells were further incubated at 33°C for two days. Cells were stabilized with SPG and lysed by one freeze-thaw cycle at -80°C. The crude cell lysate was used to infect a new Vero monolayer in order to amplify rescued viruses.

25 20. EXAMPLE 15: RESCUE OF BOVINE PARAINFLUENZA TYPE 3/HUMAN PARAINFLUENZA TYPE 3 VECTORED RESPIRATORY Syncytial VIRUS GENES BY REVERSE GENETICS

- Infectious virus was recovered by reverse genetics in HeLa or HEp-2 cells using transfection methods described previously (see Example 13). Briefly, HEp-2 or Vero cells at 30 80-90% confluence in 6 well tissue culture dishes were infected with FP-T7 or MVA-T7 at a multiplicity of infection (m.o.i.) of 0.1 - 0.3 or 1 – 5 respectively. Following infection with FP-T7 or MVA-T7, cells were washed once with PBS and transfected with the following

amounts of plasmid DNA (2.0 μ g full-length b/h PIV3 RSV F or G cDNA, 0.4 μ g pCITE/N, 0.4 μ g pCITE/P, 0.2 μ g pCITE/L). Transfections were performed in the presence of Lipofectamine2000 (Invitrogen) according to manufacturer's instruction. The transfection reactions were incubated at 33°C for 5 to 12 hours following which the media containing Lipofectamine 2000 was replaced with 2 ml of fresh OptiMEM containing gentamicin. The transfected cells were incubated further at 33°C for two days. Cells were stabilized with SPG and lysed with one freeze-thaw cycle at -80°C. The crude cell lysate was used to infect a new Vero cell monolayer in order to amplify rescued viruses. The chimeric viruses were purified by limiting dilutions in Vero cells and high titer virus stocks of 10⁶ – 10⁸ PFU/ml were generated. The RSV genes of the chimeric viruses were isolated by RT-PCR and the sequences were confirmed. Expression of the RSV proteins was confirmed by immunostaining of infected Vero cell monolayers with RSV goat polyclonal antiserum (Biogenesis).

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21. EXAMPLE 16: CONFIRMATION OF CHIMERIC BOVINE PARAINFLUENZA TYPE 3 / HUMAN PARAINFLUENZA TYPE 3 VIRUS RESCUE BY RT-PCR

To ascertain that the rescued virus is chimeric in nature, *i.e.* the virus contains hPIV3 F and HN gene sequences in a bPIV3 backbone, the viral RNA genome was analyzed further by RT-PCR. Vero cells, infected with the P1 virus stock of three independently derived isolates of b/h PIV3 were harvested and total RNA was isolated. The viral RNA was amplified using an oligo that anneals at position 4757 of bPIV3. A viral region from nt 5255 to 6255 was amplified by PCR. The resulting 1 kb PCR fragment should contain hPIV3 sequences. This was confirmed by digestion with enzymes (SacI and Bgl II) specific for hPIV3 and that do not cut in the complementary region of bPIV3 (see Figure 2). As expected, SacI and Bgl II cut the PCR fragment into smaller fragments confirming that the isolated sequences are derived from hPIV3 (see lanes 3, 5, 7). In addition, a region in the polymerase L gene from nt 9075 to nt 10469 was amplified by PCR. This region should contain bPIV3 sequences. Again the resulting 1.4 kb PCR fragment was digested using enzyme specific for bPIV3 (PvuII and BamH1) that do not cut in the equivalent region of hPIV3 (Figure 3). The 1.4 kb fragment was indeed digested by both PvuII and BamH1

confirming that the polymerase gene is bPIV3 in origin (see lanes 3, 4, 6, 7, 9 and 10 of Figure 3). In summary, the RT-PCR analysis shows that the rescued b/h PIV3 virus is chimeric in nature. It contains hPIV3 F and HN genes in a bPIV3 genetic backbone.

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**22. EXAMPLE 17: GENETIC STABILITY OF BOVINE
PARAINFLUENZA TYPE 3/HUMAN PARAINFLUENZA TYPE 3
VECTORED RESPIRATORY SYNCYTIAL VIRUS GENES**

In order to demonstrate that the b/h PIV3/RSV chimeric viruses are genetically stable and maintain the introduced RSV gene cassettes, infected cell lysates were serially blind 10 passaged ten times in Vero cells. Sub-confluent Vero cells in T25 flasks were infected with b/h PIV3/RSV at an MOI of 0.1 and incubated for 4 days at 33°C or until CPE was visible. At the end of the incubation period the infected cells and media were harvested, frozen and thawed two times, and the resulting cell lysate was used to infect a new T25 flask of Vero 15 cells. This cycle was repeated ten times. All cell lysates from P1 to P10 were analyzed by plaque assay and immunostaining with RSV polyclonal antisera for expression of RSV proteins and virus titers. At passage 10, the RSV gene cassettes were isolated by RT-PCR and the RSV gene sequences were verified by DNA sequence analysis (to identify possible nucleotide alterations). All of the isolates maintained the RSV gene cassettes and RSV protein expression for the 10 passages analyzed (data not shown).

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**23. EXAMPLE 18: VIRION FRACTIONATION OF BOVINE
PARAINFLUENZA TYPE 3/HUMAN PARAINFLUENZA TYPE 3
VECTORED RESPIRATORY SYNCYTIAL VIRUS GENES ON
SUCROSE GRADIENTS**

The question of whether the RSV proteins were incorporated into the b/h PIV3 virion 25 was investigated further by use of a biochemical assay. Vero cells were inoculated with each of the chimeric b/h PIV3/RSV viruses at an MOI of 0.1. When maximum CPE was visible, the infected monolayers were frozen, thawed, and spun for 10 minutes at 2000 rpm. The clarified supernatants were spun through a 20% sucrose cushion at 100,000 x g for 90 30 minutes. The pellet was then resuspended in PBS and layered gently on top of a 20-66% sucrose gradient. The gradients were spun at 100,000 x g for 20 hours to achieve equilibrium. Eighteen 2 ml fractions were harvested starting from the top of the gradient. 0.4 ml of each

fraction was removed for virus titer determination. Each fraction was resuspended in 2 volumes of 20% PBS and concentrated by spinning at 100,000 x g for 1 hour. The pellet was then resuspended in 0.05 ml Laemmli buffer (Biorad) and analyzed for RSV and PIV3 5 proteins by Western blot, using an RSV F MAb (NuMax L1FR-S28R), RSV (Biogenesis) and bPIV3 (VMRD) polyclonal antisera. C-terminally truncated RSV F protein expressed in baculovirus that was purified to homogeneity, was also analyzed on a sucrose gradients.

The fractions were also analyzed for peak virus titers by plaque assay. Control gradients of free RSV F (generated in baculovirus and C-terminally truncated), RSV A2, and 10 b/h PIV3 were carried out initially. The majority of free RSV F was present in fractions 3, 4, 5, and 6 in the top portion of the gradient (Figure 16A). The biggest concentration of RSV virions was observed in fractions 10, 11 and 12 (Figure 16B). The RSV fractions were probed with RSV polyclonal antiserum as well as with RSV F MAb. The fractions that contained the greatest amounts of RSV virions also showed the strongest signal for RSV F, 15 suggesting that the RSV F protein co-migrated and associated with RSV virions (Figure 16B). These fractions also displayed the highest virus titers (Figure 16B). The b/h PIV3 virions may be more pleiomorphic and thus the spread of the peak fractions containing b/h PIV3 virions was more broad. b/h PIV3 virions were present in fractions 9, 10, 11, 12, and 13 (Figure 16C). Again the fractions harboring the most amounts of virions, also displayed the 20 highest virus titers by plaque assay (Figure 16C). Sucrose gradient fractions of b/h PIV3/RSV F2 were analyzed with both a PIV3 polyclonal antiserum and an RSV F MAb (Figure 16D). The fractions containing most of the virions were fractions 11, 12, 13, and 14 as was shown by western using the PIV3 antiserum. Correspondingly, these were also the fractions that displayed the highest amounts of RSV F protein. However, some free RSV F 25 was also present in fractions 5 and 6. Fractions 11, 12, 13 and 14 displayed the peak virus titers (Figure 16D). Similarly, the fractions containing the most virions of b/h PIV3/RSV G2 (fractions 9, 10, 11, and 12) also showed the strongest signal for RSV G protein (Figure 16E). Again these were the fractions with the highest virus titers (Figure 16E). Collectively 30 these data suggested that the majority of the RSV F and G proteins co-migrated and associated with the b/h PIV3 virions. However, some free RSV proteins were also present in the top fractions of the gradients.

24. EXAMPLE 19: THE CHIMERIC BOVINE PARAINFLUENZA TYPE 3/HUMAN PARAINFLUENZA TYPE 3 VECTORED RESPIRATORY SYNCYTIAL VIRUS (RSV) COULD NOT BE NEUTRALIZED WITH RSV ANTISERA

5 In order to address the important safety question of whether the RSV surface glycoproteins incorporated into the b/h PIV3 virion resulted in an altered virus tropism phenotype, neutralization assays were carried out (Tables 6 and 7). RSV F MAbs (WHO 1200 MAb) neutralized 50% of wildtype RSV A2 at a 1:2000 dilution (Table 6). In contrast, even a dilution of 1:25 did not neutralize any of the chimeric b/h PIV3/RSV. Similarly, a 10 dilution of 1:400 of the polyclonal RSV antiserum (Biogenesis) neutralized 50% of RSV A2, but even a dilution of 1:15.6 did not neutralize b/hPIV3 RSV (Table 6).

Table 6

The b/h PIV3 RSV Chimeric Viruses are not Neutralized by RSV Antibodies

	Virus used in neutralization	Reciprocal 50% neutralizing antibody dilution		
		assay	RSV F MAb	RSV Ab
	RSV		2000	400.0
	b/h PIV3		<25	<15.6
20	b/h RSV F1*N-N		<25	<15.6
	b/h RSV F2		<25	<15.6
	b/h RSV G1		ND	<15.6
	b/h RSV G2		ND	<15.6

25 hPIV3 F MAb C191/9 neutralized 50% of b/h PIV3 as well as the b/h PIV3/RSV at a dilution of 1:500 (Table 7). An hPIV3 HN MAb 68/2 neutralized b/h PIV3 at a dilution of 1:16,000, and the b/h PIV3/RSV at a dilution of 1:32,000 (Table 7).

Table 7
The b/h PIV3 RSV Chimeric Viruses are Neutralized by hPIV3 Mabs

	Virus used in neutralization assay	Reciprocal 50% neutralizing antibody dilution	
		hPIV3 F MAb	hPIV3 HN MAb
5	RSV	62.5	<500
	b/h PIV3	500	16000
	b/h RSV F1*N-N	500	32000
	b/h RSV F2	500	32000
10	b/h RSV G1	ND ^d	32000
	b/h RSV G2	ND	32000

^d not determined.

15 **25. EXAMPLE 20: THE CHIMERIC BOVINE PIV DEMONSTRATE ATTENUATED PHENOTYPES AND ELICIT STRONG PROTECTIVE RESPONSES WHEN ADMINISTERED *IN VIVO***

Five week old Syrian Golden hamsters were infected with 5×10^5 pfu of wildtype bPIV3, recombinant bPIV3, hPIV3, human/bovine PIV3, and placebo. The five different animal groups were kept separate in micro-isolator cages. Four days post-infection, the 20 animals were sacrificed. The nasal turbinates and lungs of the animals were homogenized and stored at -80°C. Virus present in the tissues was determined by TCID₅₀ assays in MDBK cells at 37°C. Virus infection was confirmed by hemabsorption with guinea pig red blood cells. Table 8 shows the replication titers of the different PIV3 strains in hamsters in the lungs and nasal turbinates. Note that recombinant bPIV3 and the b/h PIV3 chimeric viruses 25 are attenuated in the lungs of the hamsters:

Table 8
**Replication of PIV3 Viruses in Syrian
Golden Hamsters in the Nasal Turbinates and Lungs.**

Replication of bPIV3, r-bPIV3, r-bPIV3(l), hPIV3 and Bovine/Human PIV3(l) in the Upper and Lower Respiratory Tract of Hamsters		
	Mean virus titer on day 4 postinfection (\log_{10} TCID ₅₀ /g tissue = S. E.) ^b	
Virus ^a	Nasal turbinates	Lungs
bPIV3	5.3 ± 0.3	5.3 ± 0.2
r-bPIV3	5.0 ± 0.3	3.5 ± 0.2
r-bPIV3(l)	5.5 ± 0.2	5.4 ± 0.2
hPIV3	4.9 ± 0.2	5.4 ± 0.2
Bovine/human PIV3(l)	4.9 ± 0.2	4.5 ± 0.2

^a Groups of four hamsters were inoculated intranasally with 5×10^5 PFU of indicated virus.

^b Standard error.

Furthermore, serum samples collected from the hamsters prior to infection and at day 21 post-infection were analyzed in a hemagglutination inhibition assay. The serum samples were treated with receptor destroying enzyme (RDE, DENKA Seiken Co.) and non-specific agglutinins were removed by incubation with guinea pig red blood cells for 1 hour on ice.

Wildtype bPIV3 and hPIV3 were added to two-fold serially diluted hamster serum samples. Finally, guinea pig red blood cells (0.5%) were added, and hemagglutination was allowed to occur at room temperature. Table 9 shows the antibody response generated in the hamsters upon being infected with the different PIV3 strains. Note that the b/h PIV3 chimeric virus generates as strong an antibody response against hPIV3 as does wild type hPIV3, far exceeding the response generated by the recombinant or wildtype bPIV3:

Table 9

**Hemagglutination Inhibition Assay Using Serum from
Hamsters Infected with Different PIV3 Viruses.**

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Virus Used for Inoculation of the Hamsters	Hamster Serum Titers for	
	wt bPIV3	hPIV3
Recombinant bPIV3	1:16	1:16
Wt bPIV3	1:16	1:8
Wt hPIV3	1:4	1:128
b/h PIV3 chimeric virus	1:8	1:128
Placebo	<1:4	<1.4

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These results demonstrate the properties of b/h PIV3 chimeric viruses of the present invention which make these recombinants suitable for use in vaccine formulations. Not only do the b/h PIV3 chimeric viruses demonstrate an attenuated phenotype when administered *in vivo*, but they also generate as strong an antibody response as the wildtype hPIV3. Thus, because the chimeric viruses of the present invention have a unique combination of having an attenuated phenotype and eliciting as strong an immune response as a wildtype hPIV, these chimeric viruses have the characteristics necessary for successful use in humans to inhibit and/or protect against infection with PIV.

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26. EXAMPLE 21: REPLICATION OF BOVINE PARAINFLUENZA 3/HUMAN PARAINFLUENZA 3 VECTORED RESPIRATORY SYNCYTIAL VIRUS G OR F PROTEIN IN THE UPPER AND LOWER RESPIRATORY TRACT OF HAMSTERS

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Five week old Syrian Golden hamsters (six animals per group) were infected intranasally with 1×10^6 pfu or 1×10^4 PFU of b/h PIV3, b/h PIV3/RSV, RSV A2, or placebo medium in a 100 ml volume. The different groups were maintained separately in micro-isolator cages. Four days post-infection, the nasal turbinates and lungs of the animals were harvested, homogenized and stored at -70°C. The titers of virus present in the tissues were determined by TCID₅₀ assays in Vero cells. For the challenge assays, the animals were inoculated on day 28 intranasally with 1×10^6 pfu/ml of hPIV3 or RSV A2. Four days post-

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challenge, the nasal turbinates and lungs of the animals were isolated and assayed for challenge virus replication by plaque assays on Vero cells that were immunostained for quantification. Table 10 shows the replication titers of the different strains in hamsters in the 5 lungs and nasal turbinates.

Table 10

Replication of bovine/human PIV3 Expressing the RSV G or F proteins in the Upper and Lower Respiratory Tract of Hamsters.

		Mean virus titer on day 4 postinfection (\log_{10} TCID ₅₀ /g tissue = S. E.) ^b	
Virus ^a		Nasal turbinates	Lungs
b/h PIV3		4.8 ± 0.4	4.4 ± 0.3
RSV A2		3.4 ± 0.5	3.3 ± 0.5
b/h RSV G1		4.2 ± 0.7	2.9 ± 0.7
b/h RSV F1		3.9 ± 0.4	2.7 ± 0.2
b/h RSV F1 N-P		4.6 ± 0.4	3.5 ± 0.2
b/h RSV G2		4.2 ± 0.9	4.3 ± 0.2
b/h RSV F2		4.6 ± 0.6	4.4 ± 0.5

^a Groups of four hamsters were inoculated intranasally with 5×10^6 PFU of indicated

20 virus.

^b Standard error.

Syrian Golden hamsters represent a suitable small animal model to evaluate replication and immunogenicity of recombinant bPIV3 and hPIV3 genetically engineered viruses. It was expected that the introduction of the RSV antigens would not alter the ability 25 of the chimeric b/h PIV3 to replicate in hamsters. The results showed that all of the chimeric viruses replicated to levels similar to those of b/h PIV3 in the nasal turbinates of hamsters (Table 10). In contrast, the chimeric viruses harboring the RSV genes in the first position displayed 1 – 1.5 \log_{10} reduced titers in the lungs of hamsters compared to b/h PIV3 (Table 10). The chimeric viruses containing the RSV genes in the second position replicated to 30 similar titers observed for b/h PIV3 in the lower respiratory tract of hamsters (Table 10).

**27. EXAMPLE 22: BOVINE PARAINFLUENZA 3/HUMAN
PARAINFLUENZA 3 VECTORED RESPIRATORY SYNCYTIAL
VIRUS IMMUNIZED HAMSTERS WERE PROTECTED UPON
CHALLENGE WITH HUMAN PARAINFLUENZA 3 AND
RESPIRATORY SYNCYTIAL VIRUS A2**

5 On Day 28 post-immunization, the hamsters were challenged with 1×10^6 PFU of either RSV A2 or hPIV3 to evaluate the immunogenicity induced by the b/h PIV3/RSV. Animals that received the b/h PIV3/RSV were protected completely from RSV as well as hPIV3 (Table 11). Only the animals that were administered the placebo medium displayed high titers of challenge virus in the lower and upper respiratory tracts. This assay also
10 showed that animals immunized with RSV, were not protected from challenge with hPIV3. Similarly, animals vaccinated with hPIV3 displayed high titers of the RSV challenge virus (Table 11).

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Table 11

**b/h PIV3/RSV Immunized Hamsters were
Protected Upon Challenge with hPIV3 and RSV A2**

	Challenge	hPIV3		RSV A2	
		Mean Virus Titer on Day 4	Post-challenge (\log_{10} TCID ₅₀ /g tissue ± S.E.) ^{b,c}	Mean Virus Titer on Day 4 Post-challenge (\log_{10} pfu/g tissue ± S.E.) ^b	Nasal Turbinates
5	Virus:				Lungs
10	Immunizing Virus ^a	Nasal turbinates	Lungs	Nasal Turbinates	Lungs
b/h PIV3	<1.2 ± 0.0	<1.0 ± 0.1	ND	ND	
b/h RSV G1	<1.2 ± 0.1	<1.1 ± 0.1	<1.0 ± 0.3	<0.7 ± 0.1	
b/h RSV F1	<1.2 ± 0.2	<1.0 ± 0.0	<1.1 ± 0.5	<0.6 ± 0.0	
b/h RSV F1 NP-P	<1.0 ± 0.0	<1.0 ± 0.0	<0.8 ± 0.1	<0.5 ± 0.0	
b/h RSV G2	<1.2 ± 0.2	<1.1 ± 0.2	<0.8 ± 0.1	<0.8 ± 0.3	
b/h RSV F2	<1.2 ± 0.1	<1.0 ± 0.1	<1.3 ± 0.6	<1.6 ± 1.0	
RSV A2	4.5 ± 0.6	4.8 ± 0.6	<0.6 ± 0.2	<0.6 ± 0.1	
Placebo	4.4 ± 0.1	4.1 ± 0.1	3.6 ± 0.8	3.1 ± 0.7	

^a Virus used to immunize groups of six hamsters on day 0.

20 ^b On day 28, the hamsters were challenged with 10⁶ pfu of hPIV3 or RSV A2. Four days post-challenge, the lungs and nasal turbinates of the animals were harvested.

^c Standard error.

25 28. **EXAMPLE 23: VACCINATION OF HAMSTERS WITH BOVINE PARAINFLUENZA 3/HUMAN PARAINFLUENZA 3 VECTORED RESPIRATORY SYNCYTIAL VIRUS INDUCES SERUM HAI AND NEUTRALIZING ANTIBODIES**

Prior to the challenge, serum samples were obtained on Day 28 from the immunized animals. The hamster sera were analyzed for the presence of RSV neutralizing antibodies using a 50% plaque reduction assay, and for PIV3 HAI serum antibodies by carrying out hemagglutination inhibition (HAI) assays (Table 8). 50% plaque reduction assay (neutralization assay) was carried out as follows: the hamster sera were two-fold serially

diluted, and incubated with 100 PFU of RSV A2 for one hour. Then the virus-serum mixtures were transferred to Vero cell monolayers and overlaid with methylcellulose. After 5 days of incubation at 35°C, the monolayers were immunostained using RSV polyclonal antiserum for quantification. Hemagglutination-inhibition (HAI) assays were performed by incubating serial two-fold dilutions of Day 28 hamster sera at 25°C for 30 min with hPIV3 in V-bottom 96-well plates. Subsequently, guinea pig erythrocytes were added to each well, incubation was continued for an additional 90 min, and the presence or absence of hemagglutination in each well was recorded.

10 The results showed that the viruses expressing the RSV F protein displayed RSV neutralizing antibody titers nearly as high as those observed with serum obtained from animals vaccinated with wildtype RSV (Table 12). In contrast, the viruses expressing the RSV G protein showed much lower levels of RSV neutralizing antibodies (Table 12). All of the chimeric b/h PIV3/RSV hamster sera showed levels of HAI serum antibodies that were 15 close to the levels observed for b/h PIV3 (Table 12). The results showed that the chimeric b/h PIV3 can infect and replicate efficiently in hamsters and elicit a protective immune response.

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Table 12

**Vaccination of Hamsters with b/h PIV3/RSV
Induces Serum HAI and Neutralizing Antibodies**

5	Virus ^a	Neutralizing antibody response to RSV ^{b,c} (mean reciprocal log ₂ ± SE)	HAI antibody response to hPIV3 ^c (mean reciprocal log ₂ ± SE)
	RSV	7.9 ± 1.00	ND
10	b/h RSV F1* N-N	7.8 ± 0.85	6.6 ± 0.5
	b/h RSV F1	5.5 ± 0.53	5.5 ± 0.5
	b/h RSV G1	3.4 ± 0.50	6.6 ± 0.7
	b/h RSV F2	6.9 ± 0.65	6.7 ± 0.8
	b/h RSV G2	3.4 ± 0.50	5.2 ± 0.4
	b/h PIV3	ND	7.2 ± 0.5

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^a Viruses used to immunize hamsters.

^b The neutralizing antibody titers were determined by a 50% plaque reduction assay.

^c The neutralizing antibody titers of hamster pre-serum were < 1.0 and the HAI antibody titers were < 4.0.

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29. EXAMPLE 24: VACCINATION OF HAMSTERS WITH LOW DOSE OF BOVINE PARAINFLUENZA 3/HUMAN PARAINFLUENZA 3 VECTORED RESPIRATORY SYNCYTIAL VIRUS PROTECTED HAMSTERS FROM CHALLENGE WITH RESPIRATORY SYNCYTIAL VIRUS A2, AND INDUCES SERUM HAI AND NEUTRALIZING ANTIBODIES

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In order to identify the best vaccine candidate, low dose virus with different constructs (see Example 2) were used to immunize hamsters. The results of the challenging experiments are summarized in Table 13.

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Table 13**b/h PIV3/RSV-Low Dose Immunized****Hamsters are Protected From Challenge with RSV A2**

5	Replication		Challenge with RSV A2	
	Mean Virus Titer on Day 4 Post-vaccination (\log_{10} TCID ₅₀ /g tissue ± S.E.) ^{b,c}		Mean Virus Titer on Day 4 Post-challenge (\log_{10} pfu/g tissue ± S.E.) ^b	
10	Immunizing Virus ^a	Nasal turbinates	Lungs	Nasal Turbinates Lungs
b/h PIV3	4.9 ± 0.5	4.8 ± 1.0	ND	ND
b/h RSV G1	3.0 ± 0.8	3.1 ± 0.5	< 0.9 ± 0.5	< 0.7 ± 0.4
b/h RSV F1* N-N	3.4 ± 0.1	3.5 ± 0.1	< 1.4 ± 0.7	< 0.5 ± 0.0
b/h RSV G2	4.1 ± 0.6	3.8 ± 0.4	< 0.8 ± 0.0	< 0.5 ± 0.1
15	b/h RSV F2	5.2 ± 0.6	3.9 ± 0.4	< 0.7 ± 0.1
RSV A2	2.8 ± 0.3	2.7 ± 0.6	< 0.8 ± 0.1	< 0.5 ± 0.0
Placebo	ND ^d	ND	3.0 ± 0.8	3.2 ± 0.9

^a Virus used to immunize groups of six hamsters on day 0 with a low dose of 10⁴

20 PFU/ml.

^b On day 28, the hamsters were challenged with 10⁶ pfu of RSV A2. Four days post-challenge, the lungs and nasal turbinates of the animals were harvested.

^c Standard error.

25 ^d not determined.

Next, the neutralizing antibody titers were determined by a 50% plaque reduction assay (neutralization assay). Neutralization assays were performed for b/h PIV3, b/h PIV3/RSV chimeric viruses or RSV using Vero cells. Serial two-fold dilutions of RSV polyclonal antiserum (Biogenesis; Poole, England), an RSV F MAb (WHO 1200 MAb) obtained from MedImmune or hPIV3 F (C191/9) and HN (68/2) MAbs, were incubated with approximately 100 PFU of either b/h PIV3, b/h PIV3/RSV chimeric viruses or RSV in 0.5 ml

OptiMEM at RT for 60 min. Following the incubation, virus-serum mixtures were transferred to Vero cell monolayers, incubated at 35°C for 1 hour, overlaid with 1% methyl cellulose in EMEM/L-15 medium (JRH Biosciences; Lenexa, KS) and incubated at 35°C .

- 5 Six days post-inoculation, the infected cell monolayers were immunostained. Neutralization titers were expressed as the reciprocal of the highest serum dilution that inhibited 50% of viral plaques. Neutralization assays were also carried out for serum obtained on Day 28 post-infection from hamster's immunized with b/h PIV3, b/h PIV3/RSV chimeric viruses, or RSV A2. The hamster sera were two-fold serially diluted, and incubated with 100 PFU of RSV A2 for one hour. Then the virus-serum mixtures were transferred to Vero cell monolayers and overlaid with methylcellulose. After 5 days of incubation at 35°C the monolayers were immunostained using RSV polyclonal antiserum for quantification. The neutralizing antibody titers of hamster pre-serum were < 1.0 and the HAI antibody titers were < 4.0. Hemagglutination-inhibition (HAI) assays were performed by incubating serial two-fold dilutions of Day 28 hamster sera at 25°C for 30 min with hPIV3 in V-bottom 96-well plates. Subsequently, guinea pig erythrocytes were added to each well, incubation was continued for an additional 90 min, and the presence or absence of hemagglutination in each well was recorded. Table 14 summarizes the results:

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Table 14

**Vaccination of Hamsters with Lower Doses of
b/h PIV3/RSV Induces Serum HAI and Neutralizing Antibodies**

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Virus ^a	Neutralizing antibody response to RSV ^{b,c} (mean reciprocal log ₂ ± SE)	HAI antibody response to hPIV3 ^c (mean reciprocal log ₂ ± SE)
RSV	6.5 ± 0.7	ND
b/h RSV F1* N-N	2.5 ± 0.7	5.7 ± 0.6
b/h RSV G1	2.0 ± 0.0	6.0 ± 0.0
b/h RSV F2	3.8 ± 1.5	6.7 ± 0.6
b/h RSV G2	3.8 ± 1.3	5.5 ± 0.6
b/h PIV3	ND	6.5 ± 0.7

^a Viruses used to immunize hamsters at a low dose of 10⁴ pfu/ml.

^b The neutralizing antibody titers were determined by a 50% plaque reduction assay.

^c The neutralizing antibody titers of hamster pre-serum were < 1.0 and the HAI antibody titers were < 4.0.

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The restricted replication phenotype of the chimeric viruses possessing RSV genes in the first position was exacerbated when the inoculation dose was reduced to 1 x 10⁴ PFU per animal. b/h PIV3/RSV F1 and G1 replicated in the upper respiratory tracts of hamsters to titers that were reduced by 1.0 – 2.0 log₁₀ compared to those of b/h PIV3 (Table 13). In contrast, b/h PIV3/RSV with the RSV genes in position 2, replicated in the upper respiratory tract to levels observed for b/h PIV3. Replication in the lungs of hamsters was also more restricted for the b/h PIV3/RSV harboring RSV genes in the first position (Table 13). In contrast, b/h PIV3/RSV F2 still replicated to high titers of 10^{5.2} and 10^{3.9} in the nasal turbinates and lungs, respectively (Table 13). The vaccinated hamsters were challenged on Day 28 with 1 x 10⁶ pfu of RSV A2 (Table 13). Despite the low levels of replication observed in the respiratory tracts of hamsters, the animals were protected in both the lower

and upper respiratory tract from challenge with RSV (Table 13). The degree of protection was as good as was observed for animals vaccinated with wt RSV. Only the animals that received placebo medium showed high virus titers in the nasal turbinates and lungs (Table 5 13). Serum was collected from the immunized hamsters on Day 28, and analyzed for the presence of RSV neutralizing and PIV3 HAI serum antibodies (Table 14). An approximately 50% drop in RSV neutralizing antibody titers was observed in sera obtained from hamsters immunized with b/h PIV3/RSV as compared to the titers observed for wt RSV sera (Table 10 14). But the sera obtained from animals that had received b/h PIV3 harboring the RSV genes in position 2, still displayed higher RSV neutralization antibody titers than was observed for sera from b/h PIV3/RSV with the RSV genes in position 1. The PIV3 HAI serum antibody titers were also slightly reduced compared to the b/h PIV3 sera (Table 14).

15 **30. EXAMPLE 25: BOVINE PARAINFLUENZA 3/HUMAN PARAINFLUENZA 3 VECTORED HUMAN METAPNEUMOVIRUS F IMMUNIZED HAMSTERS WERE PROTECTED UPON CHALLENGE WITH HUMAN PARAINFLUENZA VIRUS 3 OR HUMAN METAPNEUMOVIRUS NL/001**

Five groups of Syrian Golden Hamsters (each group had six hamsters) were immunized with b/h PIV3, b/h hMPV F1, b/h hMPV F2, hMPV or placebo repectively. The 20 five different animal groups were kept separate in micro-isolator cages. On Day 28 post-immunization, the hamsters were challenged with 1×10^6 PFU of either hPIV3 or hMPV (NL/001 strain) to evaluate the immunogenicity induced by the b/h PIV3/hMPV F. Four days post-challenge, the animals were sacrificed. The nasal turbinates and lungs of the animals were homogenized and stored at -80°C. Virus present in the tissues was determined 25 by TCID₅₀ assays in MDBK cells at 37°C. Virus infection was confirmed by hemabsorption with guinea pig red blood cells. Table 15 shows the replication titers of the PIV3 strain and the MPV strain in hamsters in the lungs and nasal turbinates.

Table 15

**b/h PIV3/hMPV F-Immunized Hamsters were Protected Upon Challenge with hPIV3
or hMPV/NL/001**

Challenge virus:	hPIV3		hMPV	
	Mean virus titer on day 4 post-challenge (\log_{10} TCID ₅₀ /g tissue ± S.E) ^b		Mean virus titer on day 4 post-challenge (\log_{10} PFU/g tissue ± S.E) ^b	
Immunizing virus ^a	Nasal Turbinates	Lungs	Nasal Turbinates	Lungs
b/h PIV3	< 1.3 ± 0.2	< 1.1 ± 0.1		ND
b/h hMPV F1	< 1.3 ± 0.1	< 1.1 ± 0.1	3.5 ± 0.8	< 0.5 ± 0.2
b/h hMPV F2	< 1.2 ± 0.1	< 1.2 ± 0.1	< 0.9 ± 0.4	< 0.5 ± 0.1
hMPV		ND	< 0.8 ± 0.3	< 0.4 ± 0.0
Placebo	4.3 ± 0.3	4.5 ± 0.5	6.0 ± 0.3	4.5 ± 1.3

^a Virus used to immunize groups of six hamsters on day 0.

^b On day 28, the hamsters were challenged with 10⁶ pfu of hPIV3 or hMPV. Four days post-challenge, the lungs and nasal turbinates of the animals were harvested.

ND = not determined.

The results showed that animals that received the b/h PIV3/hMPV F2 (F at position two) were protected completely from hMPV as well as hPIV3 (Table 15). However, b/h PIV3/hMPV F1 (F at position one) only reduced the titers of infected hMPV in the upper respiratory tract (e.g., nasal turbinates) by 2.5 logs, while it provided complete protection in the lower respiratory tract (e.g., the lung) from both hMPV and hPIV3 infection (Table 15). The animals that were administered the placebo medium displayed high titers of challenge virus in the lower and upper respiratory tracts (Table 15).

The present invention is not to be limited in scope by the specific described embodiments that are intended as single illustrations of individual aspects of the invention, and any constructs, viruses or enzymes that are functionally equivalent are within the scope 5 of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by 10 reference in their entireties.

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Table 16**LEGEND FOR SEQUENCE LISTING****5**

SEQ ID NO:1
and Human metapneumovirus isolate 00-1 matrix protein (M)
fusion protein (F) genes

SEQ ID NO:2 Avian pneumovirus fusion protein gene, partial cds

10 SEQ ID NO:3 Avian pneumovirus isolate 1b fusion protein
mRNA, complete cds

SEQ ID NO:4 Turkey rhinotracheitis virus gene for fusion protein (F1)
and F2 subunits), complete cds

15 SEQ ID NO:5 Avian pneumovirus matrix protein (M) gene, partial cds
and Avian pneumovirus fusion glycoprotein (F) gene,
complete cds

SEQ ID NO:6 paramyxovirus F protein hRSV B

SEQ ID NO:7 paramyxovirus F protein hRSV A2

SEQ ID NO:8 human metapneumovirus 01-71 (partial sequence)

20

SEQ ID NO:9 Human metapneumovirus isolate 00-1 matrix protein(M) and
fusion protein (F) genes

SEQ ID NO:10 Avian pneumovirus fusion protein gene, partial cds

25 SEQ ID NO:11 Avian pneumovirus isolate 1b fusion protein
mRNA, complete cds

SEQ ID NO:12 Turkey rhinotracheitis virus gene for fusion protein (F1)
and F2 subunits), complete cds

SEQ ID NO:13 Avian pneumovirus fusion glycoprotein (F) gene, complete
cds

30

SEQ ID NO:14 Turkey rhinotracheitis virus (strain CVL14/1) attachment
protein (G) mRNA, complete cds

SEQ ID NO:15 Turkey rhinotracheitis virus (strain 6574) attachment
protein (G), complete cds

5 SEQ ID NO:16 Turkey rhinotracheitis virus (strain CVL14/1) attachment
protein (G) mRNA, complete cds

SEQ ID NO:17 Turkey rhinotracheitis virus (strain 6574) attachment
protein (G), complete cds

10 SEQ ID NO:18 F protein sequence for HMPV isolate NL/1/00

SEQ ID NO:19 F protein sequence for HMPV isolate NL/17/00

SEQ ID NO:20 F protein sequence for HMPV isolate NL/1/99

SEQ ID NO:21 F protein sequence for HMPV isolate NL/1/94

15 SEQ ID NO:22 F-gene sequence for HMPV isolate NL/1/00

SEQ ID NO:23 F-gene sequence for HMPV isolate NL/17/00

SEQ ID NO:24 F-gene sequence for HMPV isolate NL/1/99

20 SEQ ID NO:25 F-gene sequence for HMPV isolate NL/1/94

SEQ ID NO:26 G protein sequence for HMPV isolate NL/1/00

SEQ ID NO:27 G protein sequence for HMPV isolate NL/17/00

25 SEQ ID NO:28 G protein sequence for HMPV isolate NL/1/99

SEQ ID NO:29 G protein sequence for HMPV isolate NL/1/94

SEQ ID NO:30 G-gene sequence for HMPV isolate NL/1/00

SEQ ID NO:31 G-gene sequence for HMPV isolate NL/17/00

30 SEQ ID NO:32 G-gene sequence for HMPV isolate NL/1/99

SEQ ID NO:33 G-gene sequence for HMPV isolate NL/1/94
SEQ ID NO:34 L protein sequence for HMPV isolate NL/1/00
5 SEQ ID NO:35 L protein sequence for HMPV isolate NL/17/00
SEQ ID NO:36 L protein sequence for HMPV isolate NL/1/99
SEQ ID NO:37 L protein sequence for HMPV isolate NL/1/94
10 SEQ ID NO:38 L-gene sequence for HMPV isolate NL/1/00
SEQ ID NO:39 L-gene sequence for HMPV isolate NL/17/00
SEQ ID NO:40 L-gene sequence for HMPV isolate NL/1/99
15 SEQ ID NO:41 L-gene sequence for HMPV isolate NL/1/94
SEQ ID NO:42 M2-1 protein sequence for HMPV isolate NL/1/00
SEQ ID NO:43 M2-1 protein sequence for HMPV isolate NL/17/00
SEQ ID NO:44 M2-1 protein sequence for HMPV isolate NL/1/99
20 SEQ ID NO:45 M2-1 protein sequence for HMPV isolate NL/1/94
SEQ ID NO:46 M2-1 gene sequence for HMPV isolate NL/1/00
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SEQ ID NO:49 M2-1 gene sequence for HMPV isolate NL/1/94
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30 SEQ ID NO:51 M2-2 protein sequence for HMPV isolate NL/17/00
SEQ ID NO:52 M2-2 protein sequence for HMPV isolate NL/1/99

SEQ ID NO:53 M2-2 protein sequence for HMPV isolate NL/1/94
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SEQ ID NO:54 M2-2 gene sequence for HMPV isolate NL/1/00
SEQ ID NO:55 M2-2 gene sequence for HMPV isolate NL/17/00
SEQ ID NO:56 M2-2 gene sequence for HMPV isolate NL/1/99
SEQ ID NO:57 M2-2 gene sequence for HMPV isolate NL/1/94
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SEQ ID NO:58 M2 gene sequence for HMPV isolate NL/1/00
SEQ ID NO:59 M2 gene sequence for HMPV isolate NL/17/00
SEQ ID NO:60 M2 gene sequence for HMPV isolate NL/1/99
15
SEQ ID NO:61 M2 gene sequence for HMPV isolate NL/1/94
SEQ ID NO:62 M protein sequence for HMPV isolate NL/1/00
SEQ ID NO:63 M protein sequence for HMPV isolate NL/17/00
20
SEQ ID NO:64 M protein sequence for HMPV isolate NL/1/99
SEQ ID NO:65 M protein sequence for HMPV isolate NL/1/94
SEQ ID NO:66 M gene sequence for HMPV isolate NL/1/00
25
SEQ ID NO:67 M gene sequence for HMPV isolate NL/17/00
SEQ ID NO:68 M gene sequence for HMPV isolate NL/1/99
SEQ ID NO:69 M gene sequence for HMPV isolate NL/1/94
30
SEQ ID NO:70 N protein sequence for HMPV isolate NL/1/00
SEQ ID NO:71 N protein sequence for HMPV isolate NL/17/00

SEQ ID NO:72 N protein sequence for HMPV isolate NL/1/99
SEQ ID NO:73 N protein sequence for HMPV isolate NL/1/94
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SEQ ID NO:75 N gene sequence for HMPV isolate NL/17/00
SEQ ID NO:76 N gene sequence for HMPV isolate NL/1/99
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SEQ ID NO:78 P protein sequence for HMPV isolate NL/1/00
SEQ ID NO:79 P protein sequence for HMPV isolate NL/17/00
15 SEQ ID NO:80 P protein sequence for HMPV isolate NL/1/99
SEQ ID NO:81 P protein sequence for HMPV isolate NL/1/94
SEQ ID NO:82 P gene sequence for HMPV isolate NL/1/00
SEQ ID NO:83 P gene sequence for HMPV isolate NL/17/00
20 SEQ ID NO:84 P gene sequence for HMPV isolate NL/1/99
SEQ ID NO:85 P gene sequence for HMPV isolate NL/1/94
SEQ ID NO:86 SH protein sequence for HMPV isolate NL/1/00
25 SEQ ID NO:87 SH protein sequence for HMPV isolate NL/17/00
SEQ ID NO:88 SH protein sequence for HMPV isolate NL/1/99
SEQ ID NO:89 SH protein sequence for HMPV isolate NL/1/94
30 SEQ ID NO:90 SH gene sequence for HMPV isolate NL/1/00
SEQ ID NO:91 SH gene sequence for HMPV isolate NL/17/00

SEQ ID NO:92 SH gene sequence for HMPV isolate NL/1/99

SEQ ID NO:93 SH gene sequence for HMPV isolate NL/1/94

5 SEQ ID NO:94 isolate NL/1/99 (99-1) HMPV (Human Metapneumovirus) cDNA sequence

SEQ ID NO:95 isolate NL/1/00 (00-1) HMPV cDNA sequence

SEQ ID NO:96 isolate NL/17/00 HMPV cDNA sequence

10 SEQ ID NO:97 isolate NL/1/94 HMPV cDNA sequence

SEQ ID NO:98 G-gene coding sequence for isolate NL/1/00 (A1)

SEQ ID NO:99 G-gene coding sequence for isolate BR/2/01 (A1)

15 SEQ ID NO:100 G-gene coding sequence for isolate FL/4/01 (A1)

SEQ ID NO:101 G-gene coding sequence for isolate FL/3/01 (A1)

SEQ ID NO:102 G-gene coding sequence for isolate FL/8/01 (A1)

20 SEQ ID NO:103 G-gene coding sequence for isolate FL/10/01 (A1)

SEQ ID NO:104 G-gene coding sequence for isolate NL/10/01 (A1)

SEQ ID NO:105 G-gene coding sequence for isolate NL/2/02 (A1)

25 SEQ ID NO:106 G-gene coding sequence for isolate NL/17/00 (A2)

SEQ ID NO:107 G-gene coding sequence for isolate NL/1/81 (A2)

SEQ ID NO:108 G-gene coding sequence for isolate NL/1/93 (A2)

30 SEQ ID NO:109 G-gene coding sequence for isolate NL/2/93 (A2)

SEQ ID NO:110 G-gene coding sequence for isolate NL/3/93 (A2)

SEQ ID NO:111 G-gene coding sequence for isolate NL/1/95 (A2)

SEQ ID NO:112 G-gene coding sequence for isolate NL/2/96 (A2)

5 SEQ ID NO:113 G-gene coding sequence for isolate NL/3/96 (A2)

SEQ ID NO:114 G-gene coding sequence for isolate NL/22/01 (A2)

SEQ ID NO:115 G-gene coding sequence for isolate NL/24/01 (A2)

10 SEQ ID NO:116 G-gene coding sequence for isolate NL/23/01 (A2)

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SEQ ID NO:118 G-gene coding sequence for isolate NL/3/02 (A2)

15 SEQ ID NO:119 G-gene coding sequence for isolate NL/1/99 (B1)

SEQ ID NO:120 G-gene coding sequence for isolate NL/11/00 (B1)

SEQ ID NO:121 G-gene coding sequence for isolate NL/12/00 (B1)

20 SEQ ID NO:122 G-gene coding sequence for isolate NL/5/01 (B1)

SEQ ID NO:123 G-gene coding sequence for isolate NL/9/01 (B1)

SEQ ID NO:124 G-gene coding sequence for isolate NL/21/01 (B1)

25 SEQ ID NO:125 G-gene coding sequence for isolate NL/1/94 (B2)

SEQ ID NO:126 G-gene coding sequence for isolate NL/1/82 (B2)

SEQ ID NO:127 G-gene coding sequence for isolate NL/1/96 (B2)

SEQ ID NO:128 G-gene coding sequence for isolate NL/6/97 (B2)

30 SEQ ID NO:129 G-gene coding sequence for isolate NL/9/00 (B2)

SEQ ID NO:130 G-gene coding sequence for isolate NL/3/01 (B2)

SEQ ID NO:131 G-gene coding sequence for isolate NL/4/01 (B2)

5 SEQ ID NO:132 G-gene coding sequence for isolate UK/5/01 (B2)

SEQ ID NO:133 G-protein sequence for isolate NL/1/00 (A1)

SEQ ID NO:134 G-protein sequence for isolate BR/2/01 (A1)

10 SEQ ID NO:135 G-protein sequence for isolate FL/4/01 (A1)

SEQ ID NO:136 G-protein sequence for isolate FL/3/01 (A1)

SEQ ID NO:137 G-protein sequence for isolate FL/8/01 (A1)

15 SEQ ID NO:138 G-protein sequence for isolate FL/10/01 (A1)

SEQ ID NO:139 G-protein sequence for isolate NL/10/01 (A1)

SEQ ID NO:140 G-protein sequence for isolate NL/2/02 (A1)

SEQ ID NO:141 G-protein sequence for isolate NL/17/00 (A2)

20 SEQ ID NO:142 G-protein sequence for isolate NL/1/81 (A2)

SEQ ID NO:143 G-protein sequence for isolate NL/1/93 (A2)

SEQ ID NO:144 G-protein sequence for isolate NL/2/93 (A2)

25 SEQ ID NO:145 G-protein sequence for isolate NL/3/93 (A2)

SEQ ID NO:146 G-protein sequence for isolate NL/1/95 (A2)

SEQ ID NO:147 G-protein sequence for isolate NL/2/96 (A2)

30 SEQ ID NO:148 G-protein sequence for isolate NL/3/96 (A2)

SEQ ID NO:149 G-protein sequence for isolate NL/22/01 (A2)

SEQ ID NO:150 G-protein sequence for isolate NL/24/01 (A2)

SEQ ID NO:151 G-protein sequence for isolate NL/23/01 (A2)

5 SEQ ID NO:152 G-protein sequence for isolate NL/29/01 (A2)

SEQ ID NO:153 G-protein sequence for isolate NL/3/02 (A2)

SEQ ID NO:154 G-protein sequence for isolate NL/1/99 (B1)

10 SEQ ID NO:155 G-protein sequence for isolate NL/11/00 (B1)

SEQ ID NO:156 G-protein sequence for isolate NL/12/00 (B1)

SEQ ID NO:157 G-protein sequence for isolate NL/5/01 (B1)

15 SEQ ID NO:158 G-protein sequence for isolate NL/9/01 (B1)

SEQ ID NO:159 G-protein sequence for isolate NL/21/01 (B1)

SEQ ID NO:160 G-protein sequence for isolate NL/1/94 (B2)

20 SEQ ID NO:161 G-protein sequence for isolate NL/1/82 (B2)

SEQ ID NO:162 G-protein sequence for isolate NL/1/96 (B2)

SEQ ID NO:163 G-protein sequence for isolate NL/6/97 (B2)

25 SEQ ID NO:164 G-protein sequence for isolate NL/9/00 (B2)

SEQ ID NO:165 G-protein sequence for isolate NL/3/01 (B2)

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SEQ ID NO:167 G-protein sequence for isolate NL/5/01 (B2)

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SEQ ID NO:194 F-gene coding sequence for isolate NL/7/02
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SEQ ID NO:198 F-gene coding sequence for isolate NL/1/93
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SEQ ID NO:225 F-gene coding sequence for isolate FL/2/01
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30 SEQ ID NO:246 F-gene coding sequence for isolate NL/12/02

SEQ ID NO:247 F-gene coding sequence for isolate HK/1/02

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SEQ ID NO:254 F-protein sequence for isolate FL/4/01

15 SEQ ID NO:255 F-protein sequence for isolate FL/8/01

SEQ ID NO:256 F-protein sequence for isolate UK/1/01

SEQ ID NO:257 F-protein sequence for isolate UK/7/01

SEQ ID NO:258 F-protein sequence for isolate FL/10/01

20 SEQ ID NO:259 F-protein sequence for isolate NL/6/01

SEQ ID NO:260 F-protein sequence for isolate NL/8/01

SEQ ID NO:261 F-protein sequence for isolate NL/10/01

25 SEQ ID NO:262 F-protein sequence for isolate NL/14/01

SEQ ID NO:263 F-protein sequence for isolate NL/20/01

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15 SEQ ID NO:294 F-protein sequence for isolate NL/2/99
SEQ ID NO:295 F-protein sequence for isolate NL/3/99
SEQ ID NO:296 F-protein sequence for isolate NL/11/00
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SEQ ID NO:300 F-protein sequence for isolate NL/9/01
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SEQ ID NO:305 F-protein sequence for isolate FL/2/01

SEQ ID NO:306 F-protein sequence for isolate FL/5/01
SEQ ID NO:307 F-protein sequence for isolate FL/7/01
5 SEQ ID NO:308 F-protein sequence for isolate FL/9/01
SEQ ID NO:309 F-protein sequence for isolate UK/10/01
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10 SEQ ID NO:311 F-protein sequence for isolate NL/1/94
SEQ ID NO:312 F-protein sequence for isolate NL/1/96
SEQ ID NO:313 F-protein sequence for isolate NL/6/97
15 SEQ ID NO:314 F-protein sequence for isolate NL/7/00
SEQ ID NO:315 F-protein sequence for isolate NL/9/00
SEQ ID NO:316 F-protein sequence for isolate NL/19/00
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SEQ ID NO:318 F-protein sequence for isolate NL/3/01
SEQ ID NO:319 F-protein sequence for isolate NL/4/01
25 SEQ ID NO:320 F-protein sequence for isolate NL/11/01
SEQ ID NO:321 F-protein sequence for isolate NL/15/01
SEQ ID NO:322 F-protein sequence for isolate NL/18/01
SEQ ID NO:323 F-protein sequence for isolate FL/6/01
30 SEQ ID NO:324 F-protein sequence for isolate UK/5/01

SEQ ID NO:325 F-protein sequence for isolate UK/8/01

SEQ ID NO:326 F-protein sequence for isolate NL/12/02

5 SEQ ID NO:327 F-protein sequence for isolate HK/1/02

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WHAT IS CLAIMED IS:

1. A chimeric bovine parainfluenza virus type 3 comprising a heterologous
5 nucleotide sequence encoding a metapneumovirus polypeptide.
2. A chimeric human parainfluenza virus type 3 comprising a heterologous
nucleotide sequence encoding a metapneumovirus polypeptide.
10
3. A chimeric bovine parainfluenza virus type 3/human parainfluenza virus type 3
comprising a heterologous nucleotide sequence encoding a metapneumovirus polypeptide.
15
4. The virus of claim 1, 2, or 3, wherein said virus comprises heterologous nucleotide
sequences derived from the same gene of a metapneumovirus.
20
5. The virus of claim 1, 2, or 3, wherein said virus comprises heterologous
nucleotide sequences derived from at least two different genes of a metapneumovirus.
25
6. The virus of claim 1, 2, or 3, wherein one or more of the open reading frames in
the genome of the virus have been replaced by an ORF which encodes one or more of (i) an
avian pneumovirus (APV) F protein; (ii) an APV G protein; (iii) an APV SH protein; (iv) an
APV N protein; (v) an APV P protein; (vi) an APV M2 protein; (vii) an APV M2-1 protein;
(viii) an APV M2-2 protein; or (ix) an APV L protein.
30
7. The virus of claim 1, 2, or 3, wherein one or more of the open reading frames in
the genome of virus have been replaced by an ORF which encodes one or more of (i) a
mammalian metapneumovirus (MPV) F protein; (ii) a mammalian MPV G protein; (iii) a

mammalian MPV SH protein; (iv) a mammalian MPV N protein; (v) a mammalian MPV P protein; (vi) a mammalian MPV M2 protein; (vii) a mammalian MPV M2-1 protein; (viii) a mammalian MPV M2-2 protein; or (ix) a mammalian MPV L protein.

5

8. The virus of claim 6, wherein the avian pneumovirus is APV type A, APV type B, APV type C, or APV type D.

10

9. The virus of claim 7, wherein the mammalian MPV is variant A1, variant A2, variant B1, or variant B2.

15

10. The virus of claim 1, 2, or 3, wherein said heterologous nucleotide sequence is added to the complete genome of said virus.

15

11. The virus of claim 1, 2, or 3, wherein said nucleotide sequence is added at a nucleotide position of the parainfluenza virus genome of 104, 1774, and 3724.

20

12. The virus of claim 1, 2, or 3, wherein a nucleotide sequence of said parainfluenza virus has been substituted by said heterologous nucleotide sequence.

25

13. The virus of claim 1, 2, or 3, wherein the heterologous sequences are inserted into the genome of said parainfluenza virus, wherein the genome has been deleted of one or more genes.

30

14. The virus of claim 1, wherein said bovine parainfluenza virus is a Kansas-strain bovine parainfluenza virus type 3.

15. The virus of claim 1, 2, or 3, wherein said heterologous nucleotide sequence is derived from the nucleotide sequences encoding a F protein, a G protein or a fragment thereof.

5

16. The virus of claim 15, wherein said F protein comprises an ectodomain of a F protein of a metapneumovirus, a transmembrane domain of a F protein of a parainfluenza virus, and luminal domain of a F protein of a parainfluenza virus.

10

17. The virus of claim 1, 2, or 3, wherein said nucleotide sequence is SEQ ID Nos:1 to 5, 14, or 15.

15

18. The virus of claim 1, 2, or 3, wherein said nucleotide sequence encodes a protein of SEQ ID Nos: 6 to 13, 16, or 17.

20

19. The virus of claim 1, 2, or 3, wherein said virus further comprises a heterologous nucleotide sequence derived from a respiratory syncytial virus or a mutated form of respiratory syncytial virus.

25

20. The virus of claim 19, wherein the respiratory syncytial virus is a respiratory syncytial virus type A, a respiratory syncytial virus type B, a bovine respiratory syncytial virus, or an ovine respiratory syncytial virus.

30

21. The virus of claim 19, wherein said sequence is derived from the nucleotide sequences encoding a F protein, a G protein or a fragment thereof of said respiratory syncytial virus.

22. The chimeric parainfluenza virus of claim 1, 2, or 3, wherein the genome of said virus contains mutations or modifications, in addition to said heterologous nucleotide sequences, which result in a chimeric virus having a phenotype more suitable for use in
5 vaccine formulations such as an attenuated phenotype or a phenotype with enhanced antigenicity.

23. The chimeric parainfluenza virus of claim 1, 2, or 3, wherein the intergenic region of said heterologous nucleotide sequence is altered.
10

24. The chimeric parainfluenza virus of claim 1, 2, or 3, wherein said heterologous nucleotide sequence is added at a position of the parainfluenza virus genome selected from the group consisting of position 1, 2, 3, 4, 5, and 6, and wherein the intergenic region of said
15 heterologous nucleotide sequence is altered.

25. A recombinant DNA or RNA molecule encoding the genome of the virus of claim 1, 2, or 3.
20

26. A recombinant DNA or RNA molecule encoding the genome of the virus of claim 18.
25

27. A vaccine formulation comprising the chimeric virus of claim 1, 2, or 3, and a pharmaceutically acceptable excipient.
30

28. A vaccine formulation comprising the chimeric virus of claim 18 and a pharmaceutically acceptable excipient.

29. The vaccine formulation of claim 27, wherein said chimeric virus comprises a genomic modification or mutation which results in an attenuated phenotype or enhanced antigenicity.

5

30. The vaccine formulation of claim 29, wherein said modification or mutation is derived from a naturally occurring mutant.

10

31. The vaccine formulation of claim 27, wherein said vaccine is used to modulate the immune response of humans, primates, horses, cows, sheep, pigs, goats, dogs, cats, avian species or rodents.

15

32. The vaccine formulation of claim 30, wherein the vaccine is used to modulate the immune response of a human infant or a child.

20

33. An immunogenic formulation comprising the chimeric virus of claim 1, 2, or 3, and a pharmaceutically acceptable excipient.

25

34. An immunogenic formulation comprising the chimeric virus of claim 18 and a pharmaceutically acceptable excipient.

30

35. The immunogenic formulation of claim 33, wherein said chimeric virus comprises a genomic modification or mutation which results in an attenuated phenotype or enhanced antigenicity.

36. The immunogenic formulation of claim 35, wherein said modification or mutation is derived from a naturally occurring mutant.

37. The vaccine formulation of claim 33, wherein said vaccine is used to modulate the immune response of humans, primates, horses, cows, sheep, pigs, goats, dogs, cats, avian species or rodents.

5

38. The vaccine formulation of claim 36, wherein the vaccine is used to modulate the immune response of a human infant or a child.

10

39. A method for treating or preventing a respiratory tract infection in a mammal, said method comprising administering a vaccine of claim 27.

15

40. The method of claim 39, wherein the respiratory tract infection is a MPV infection.

20

41. The method of claim 39, wherein the respiratory tract infection is an infection with MPV, RSV, hPIV or a combination thereof.

25

42. The method of claim 39, wherein the subject is a human.

43. The method of claim 42, wherein the human subject is less than 5 years of age.

30

44. The method of claim 42, wherein the human subject is less than 2 years of age.

45. The method of claim 42, wherein the human subject suffers from a disease or a condition in addition to the respiratory tract infection.

46. The method of claim 45, wherein the disease or a condition is of cystic fibrosis, leukemia, non-Hodgkin lymphoma, asthma, and bone marrow transplantation and kidney transplantation.

5

47. The human subject of claim 42, wherein the human subject is an immunocompromised individual.

10

48. The human subject of claim 42, wherein the human subject is an elderly.

15

20

25

30

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Human	1	MSWKVVIIFSLITPQHGLKESYLEESCSTITEGYLSVLRTGWTNVFTLEVDVENLTC	60
		MSWKVW++ LL TP GL+ESYLEESCST+T GYLSVLRTGWTNVFTLEVDVENLTC	
Avian	1	MSWKVVLLLVLLATPTGGLEESYLEESCSTVTRGYLSVLRTGWTNVFTLEVDVENLTC	60
Human	61	ADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRQSRFVLGAIALGVATAAVTA	120
		DGPSLI+TEL+LTK+AL EL+TV ADQLA+E +I +PR++RFVLGAIALGVAT AAVTA	
Avian	61	TDGPSLIRTELELTKNALEELKTVPADQLAKEARIMSPRKRKFVLGAIALGVATTAAVTA	120
Human	121	GVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNNGVRVLATAVRELKDFVSKNLTRAINKN	180
		GVAIAKTIRLE EV A1+ AL+ TNEAVSTLGNNGVRVLATAV +LKDF+SK LT AINKN	
Avian	121	GVAIAKTIRLEGEVAAIRGALRNTNEAVSTLGNNGVRVLATAVNDLKDFISKKLTPAINKN	180
Human	181	KCDIADLKMVASFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQ	240
		KCDI+DLKMASF Q+NRRFLNVVRQFSDNAGITPAISLDLMTDAEL RAVSNMPTS+GQ	
Avian	181	KCDISDLKMVASFGQYNRRFLNVVRQFSDNAGITPAISLDLMTDAELVRAVSNMPTSSGQ	240
Human	241	IKLMLENRAMRRKGFGFLIGVYGSIVIYMQLPIFGVIDTPCWIVKAAPSCSGKKGNYA	300
		I LMLENRAMRRKGFG LIGVYG SV+YMVQLPIFGVIDTPCW VKAAP CSGK G+YA	
Avian	241	INLMLENRAMRRKGFGILIGVYGGSVVYMQLPIFGVIDTPCWVKVKAAPLCSGKDGSYA	300
Human	301	CLLREDQGWYCQNAGSTVYYPPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYP	360
		C LREDQGWYCQNAGSTVYYPPNE+DC R DHVFCDTAAGINVA++S+ECN NISTT YP	
Avian	301	CPLREDQGWYCQNAGSTVYYPNEEDCVVRSDHVFCDTAAGINVAKESEEERNISTTKYP	360
Human	361	CKVSTGRHPISMVALSPLGALVACYKGVSIGNSNRVGIIKQLNKGSYITNQDADTVTI	420
		CKVSTGRHPISMVALSPLGALVACY GVSCSIGSN+VGI+ L KGCSYI+NQDADTVTI	
Avian	361	CKVSTGRHPISMVALSPLGALVACYDGVSIGSNKVGIIIRRLGKGCSYISNQDADTVTI	420
Human	421	DNTVYQLSKVEGEQHVIKGRPVSSEDVFKFPEDQFNVALDQVFESIENSQALVDQSNRI	480
		DNTVYQLSKVEGEQH IKG+PVSS+FDP++FPEDQFN+ALDQVFES+E S+ L+DQSN+I	
Avian	421	DNTVYQLSKVEGEQHTIKGKPVSNNFDPIEFPEDQFNIALDQVFESVEKSKNLIDQSNKI	480
Human	481	LSSAEKGNTGFIIVIILIAVLGSTMILVSFIIIKKTKRPTGAPPESGVTN	532
		L S EKGN GF+IVI LI +L + V +F ++KK K P E++GV N	
Avian	481	LDSTEKGNAGFVIVIALIVLLMLAVGVGIFFVVKKRKAAPKFPMEMNGVNN	532

FIG. 1A

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Human	1	MSWKVVIIFSLLITPQHGLKESYLEESCSTITEGYLSVLRTGWYTNVFTLEVQDVENLTC	60
	M ++ ++ L+ P ++E+Y EESCST+T GY S VLRTGWYTNVF LE+G+VEN+TC		
Turkey	1	MDVRICLLLFLISNPSSCIQETYNEESCSTVTRGYKSVLRTGWYTNVFNLEIGNVENITC	60
Human	61	ADGPSLIKTELDLTKSALRELRTVSADQLAREEQIENPRQSRFVLGAIALGVATAAAVTA	120
	DGPSLI TEL LTK+ALREL+TVSADQ+A+E ++ +PR+ RFVLGAIALGVATAAAVTA		
Turkey	61	NDGPSLIDTELVLTKNALRELRTVSADQVAKESRLSSPRRRFVLGAIALGVATAAAVTA	120
Human	121	GVAIAKTIRLESEVTAIKNALKKTNEAVSTLGNGV~VLATAVRELKDFVSKNLTRAINKN	180
	GVA+AKTIRLE EV AIKNAL+ TNEAVSTLGNGVRLATAV +LK+F+SK LT AIN+N		
Turkey	121	GVALAKTIRLEGEVKAIKNALRNTNEAVSTLGNGVRLATAVNDLKEFISKKLTPAINQN	180
Human	181	KCDIADLKMAVSFSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQ	240
	KC+IAD+KMA+SF Q NRRFLNVVRQFSD+AGIT A+SLDLMTD EL RA++ MPTS+GQ		
Turkey	181	KCNIADIKAISFGQNNRRFLNVVRQFSDSAGITSAVSLDLMTDELVRAINRMPTSSGQ	240
Human	241	IKLMLENRAMVRRKGFGFLIGVYGSIVIYMQLPIFGVIDTPCWIVKAAPSCSGKKGNYA	300
	I LML NRAMVRRKGFG LIGVY +V+YMVQLPIFGVI+TPCW 'V AAP C +KGNYA		
Turkey	241	ISLMLNNRAMVRRKGFGILIGVYDGTVVYMVQLPIFGVIETPCWRVVAAPLCRKEKGNYA	300
Human	301	CLLRDQGWYCQNAGSTVYPNEKDCETRGDHVFCDTAAGINVAEQSKECNINISTTNYP	360
	C+LREDQGWYC NAGST YYPN+ DCE R D+VFCDTAAGINV A + ++CN NIST+ YP		
Turkey	301	CILREDQGWYCTNAGSTAYPNKDDCEVRDDYVFCDTAAGINVALEVEQCNYNISTSKYP	360
Human	361	CKVSTGRHPISMVALSPLGALVACYKGVCSIGSNRVGIIKQLNKGSYITNQDADTVTI	420
	CKVSTGRHP+SMVAL+PLG LV+CY+ VSCSIGSN+VGIKQL KGC++I N +ADT+TI		
Turkey	361	CKVSTGRHPVSMVALTPLGGLVSCYESVCSIGSNKVGIIKQLGKGCTHIPNNEADTITI	420
Human	421	DNTVYQLSKVEGEQHVIKGRPVSSFDPKFPEDQFVALIDQVFESIENSQALVDQSNRI	480
	DNTVYQLSKV GEQ IKG PV ++F+P+ FPEDQFVALIDQVFESI+ SQ L+D+SN +		
Turkey	421	DNTVYQLSKVVEQRТИKGAPVNNFNPILFPEDQFVALIDQVFESIDRSQDLIDKSNDL	480
Human	481	LSSAEKGNTGFIIVIILIAVLGSTMILVSFII--IKKTKRPTGAPP else GVTNNGFI	536
	L + K G I I++ +LG +L ++ ++KTK P P +G ++ ++		
Turkey	481	LGADAKSKAGIAIAIVVLVILGIFFLAVIYYCSRVRKTK-PKHDYPATTGHSSMAYV	537

FIG. 1B

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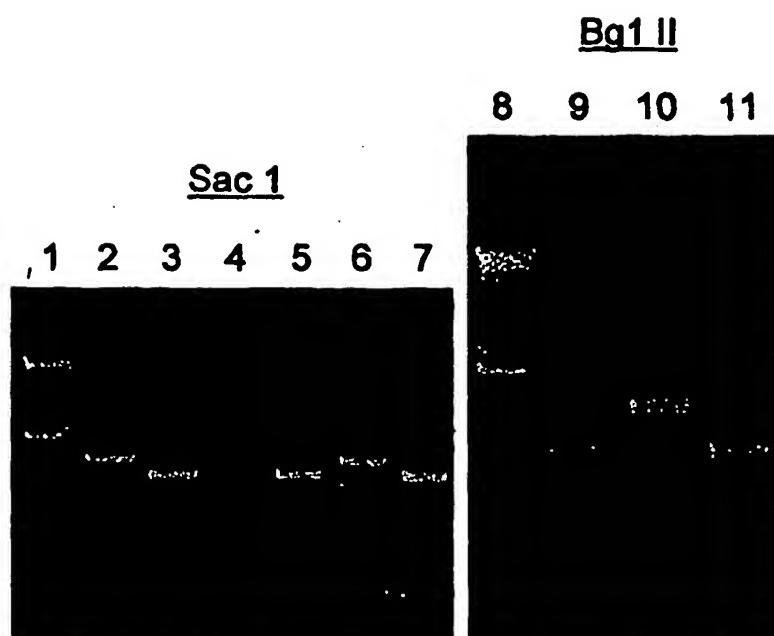


FIG.2

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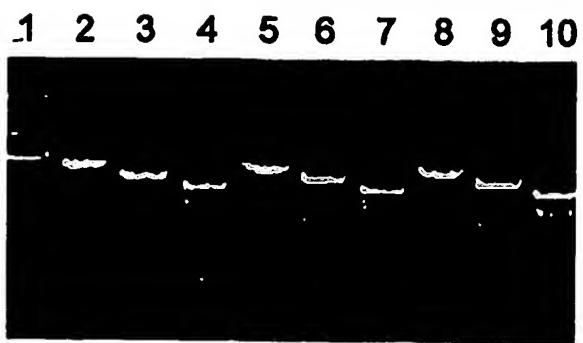
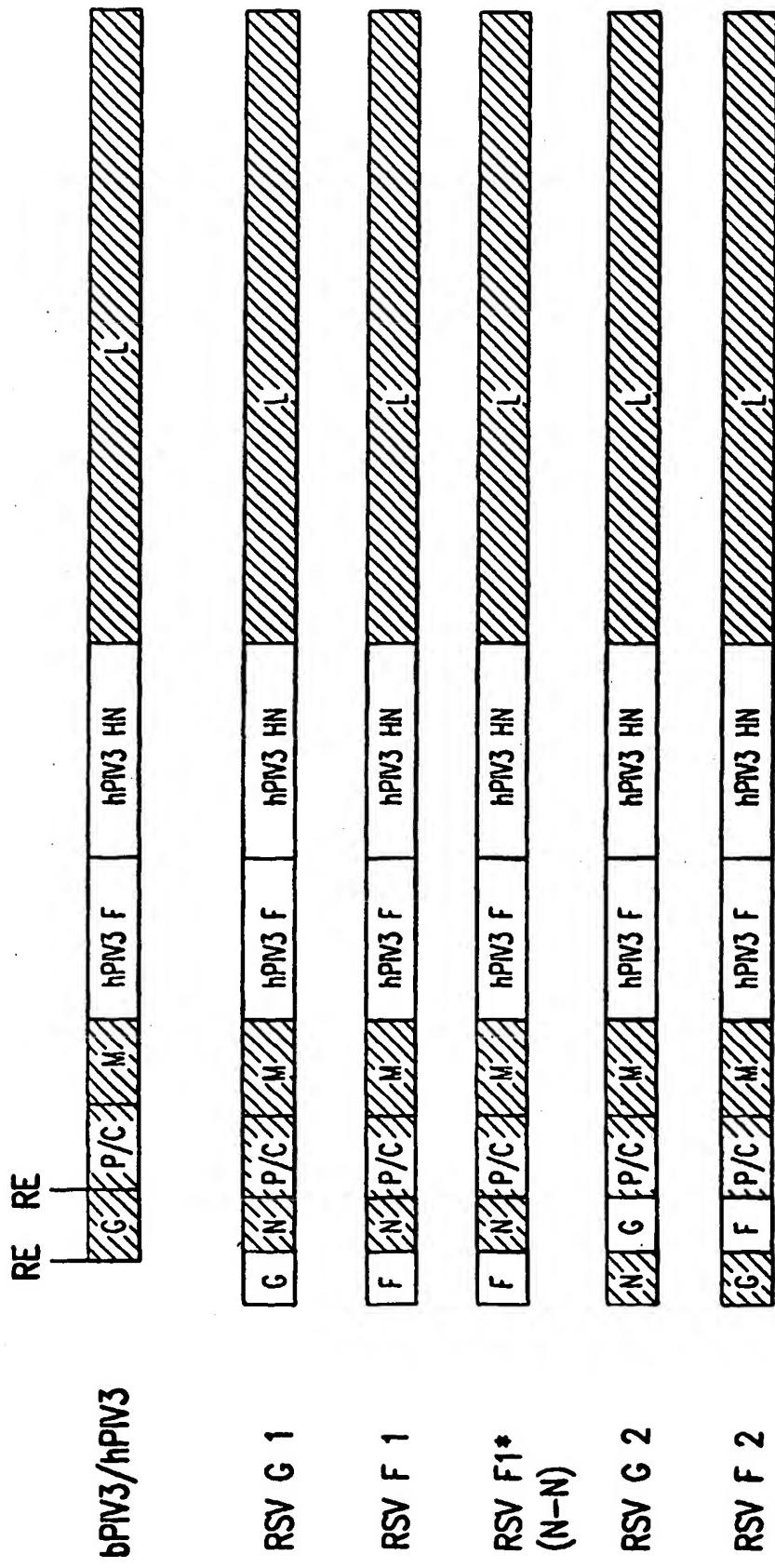


FIG.3

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Rescued bPIV3/hPIV3-Vectored RSV Constructs

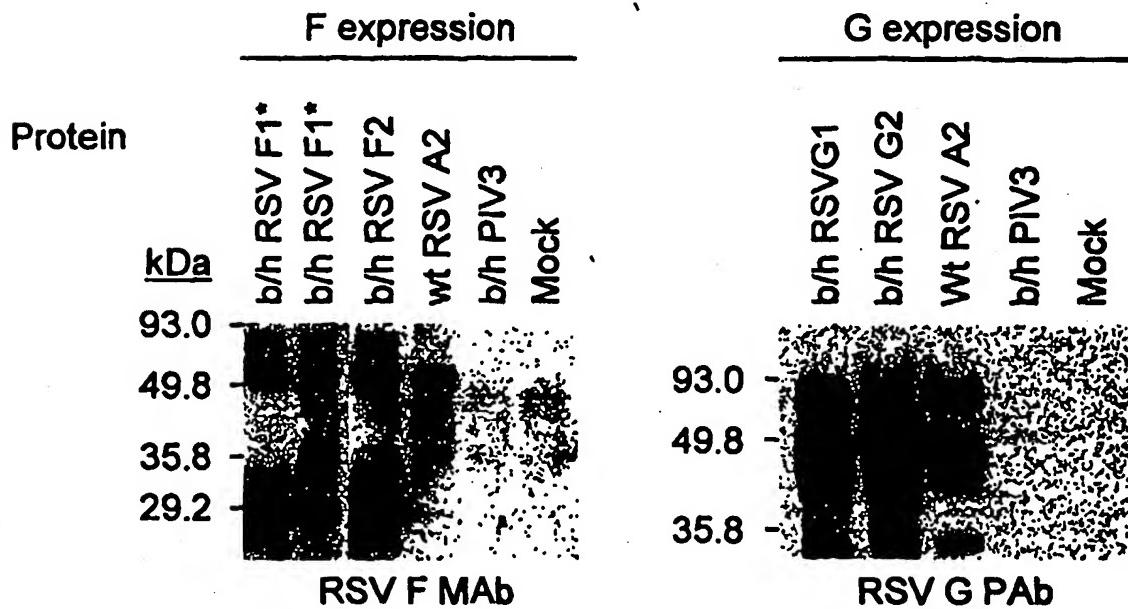


Note: all RSV genes are linked to the bPIV3 N-P intergenic region with the exception of RSV F1* which is followed by the shorter bPIV3 N gene stop/N gene start sequences.

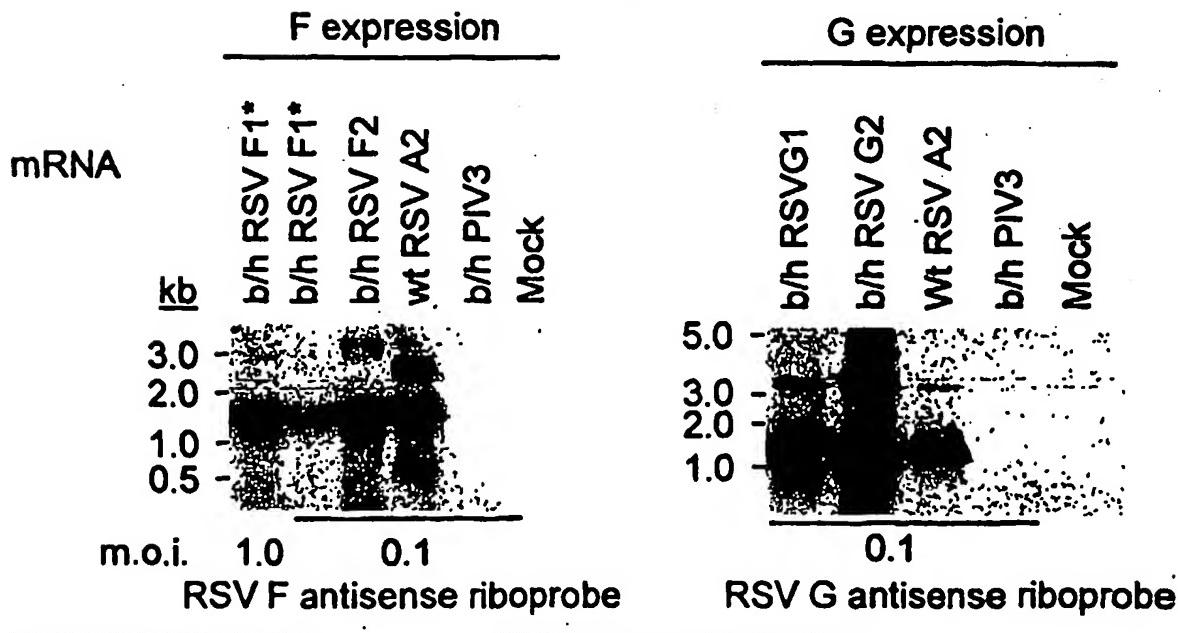
FIG. 4

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**Expression of RSV F and G
Proteins from Chimeric Bovine/Human PIV3**

**FIG.5(A)**

**Expression of RSV F and G mRNAs
from Chimeric Bovine/Human PIV3**



b/h PIV3/RSV F1(N-N)

48 hours post-infection

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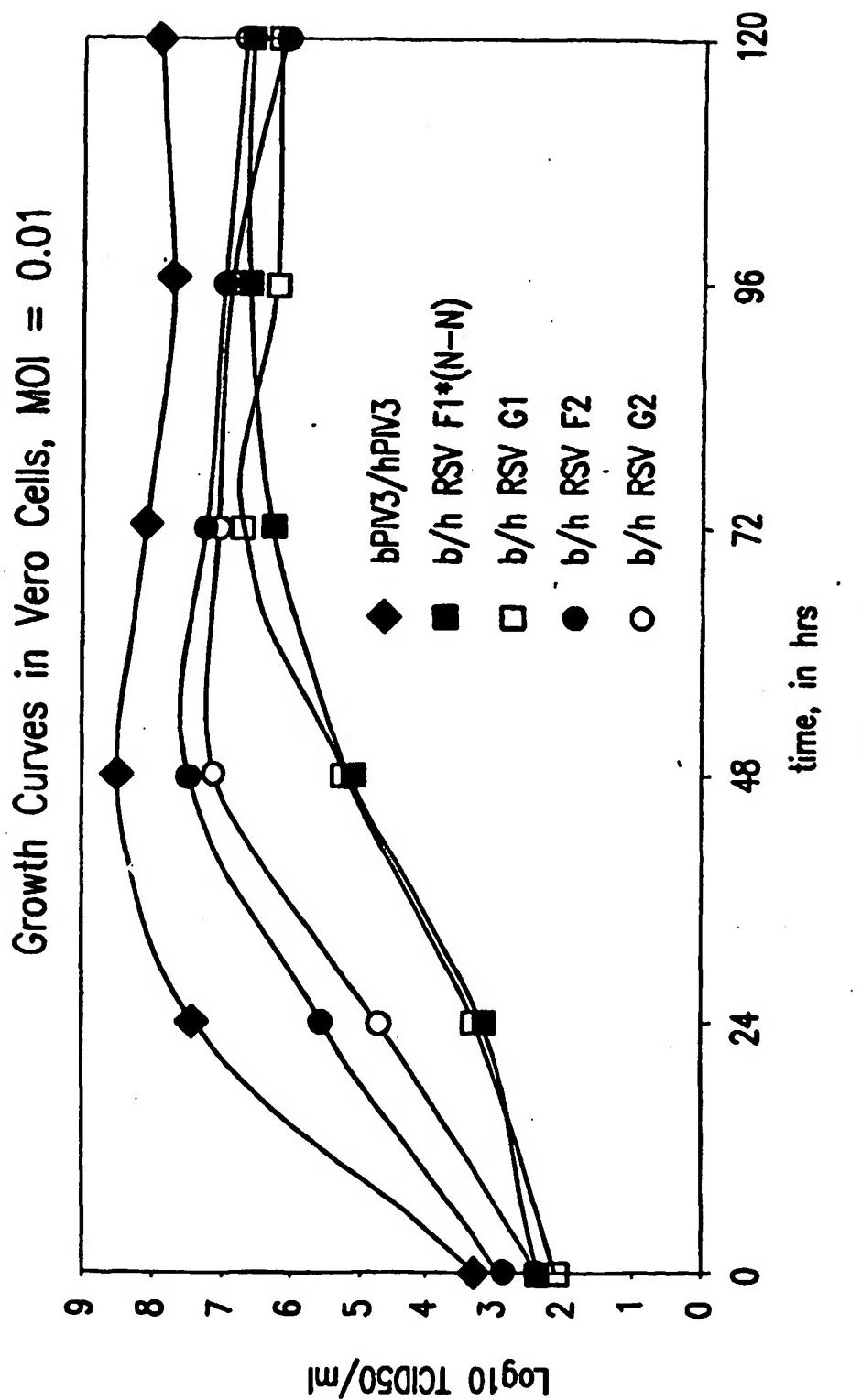


FIG. 5(C)

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**Positional Effect of eGFP Insertions in the PV3
Genome on Virus Replication**



Status: virus stocks prepared

Titer: 4×10^8 PFU/ml



Status: virus stocks prepared

Titer: 3×10^8 PFU/ml



Status: virus stocks prepared

Titer: 1.1×10^7 PFU/ml



Status: virus rescued, biological cloning in progress.

b/h GFP5 and b/h GFP 6 construction in progress.

FIG. 6

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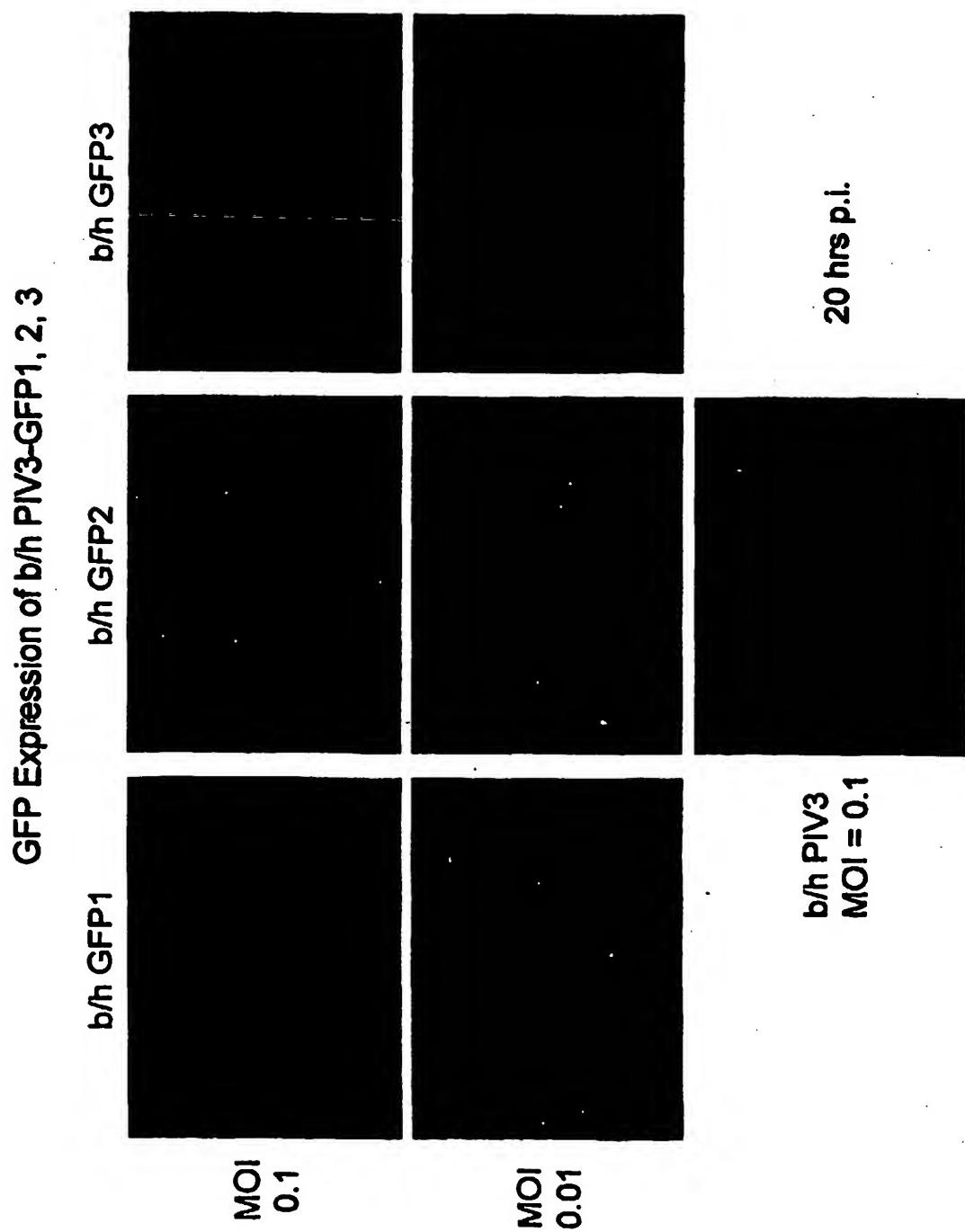
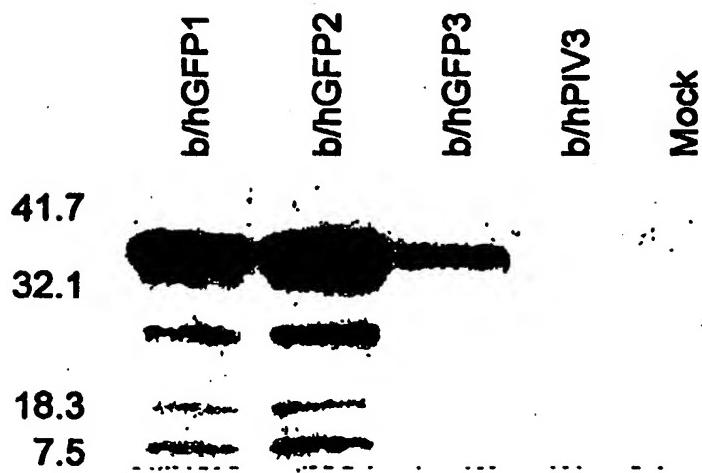


FIG. 7(A)

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eGFP Expression in b/h PIV3 in Positions
1, 2 and 3



MOI of 0.1 in Vero cells
24 hours post-infection

FIG. 7(B)

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Growth Curves for b/h PIV3/GFP1, 2, and 3
in Vero Cells, MOI = 0.1

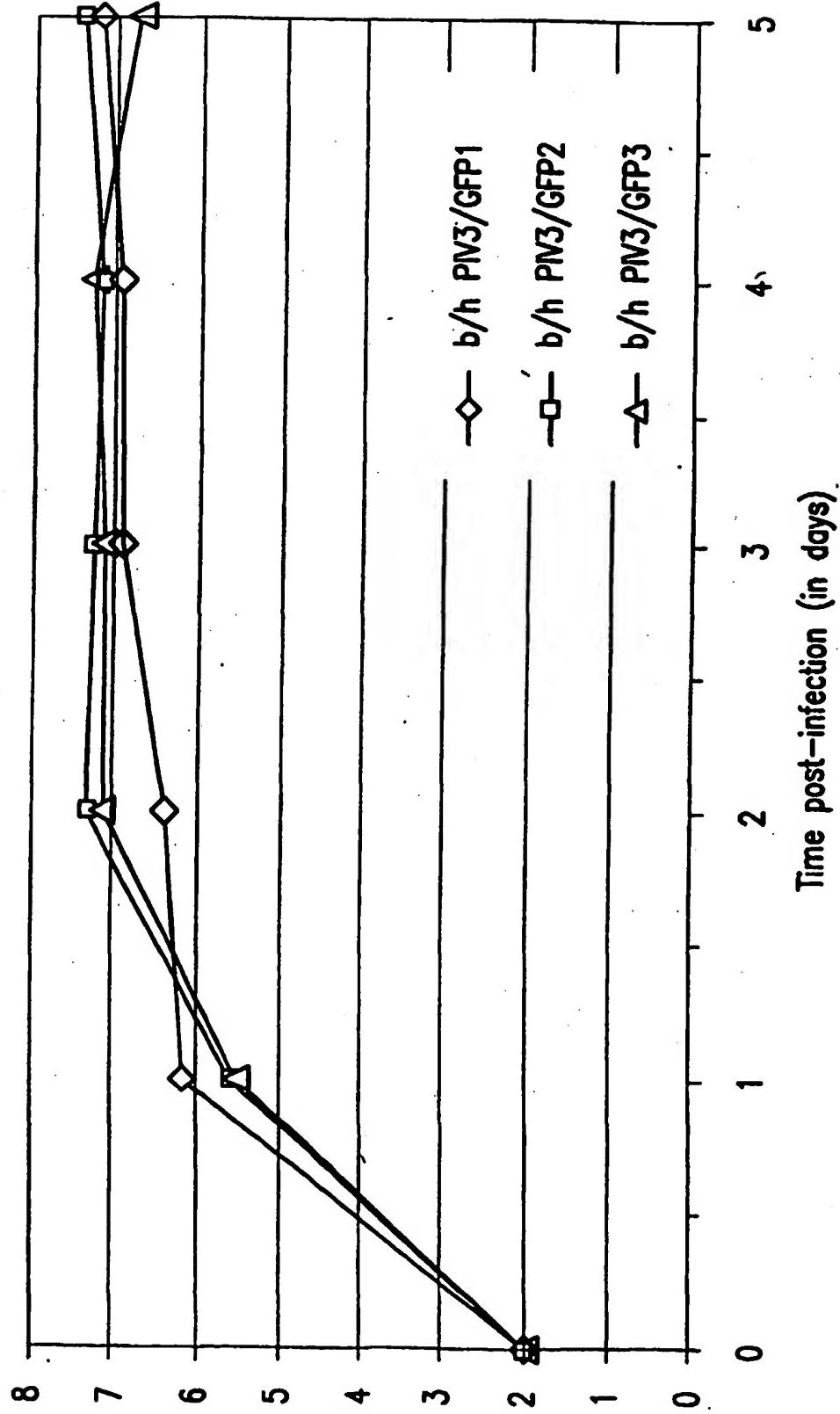
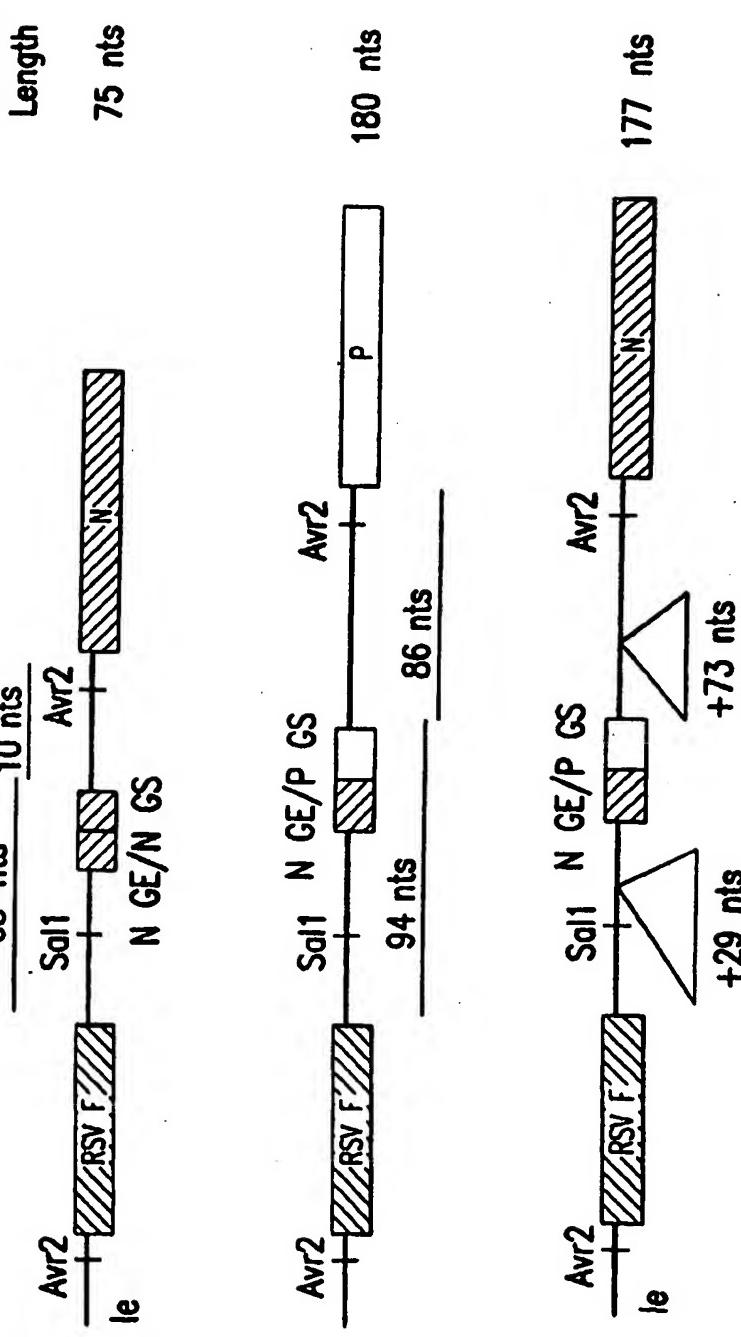


FIG. 7(C)

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**Differences between b/h PIV3 RSV F1* and
b/h PIV3 RSV F2 Intergenic Regions**



SUBRSV F1*
SUBRSV F2
SUBRSV F1

N-N
N-P
N-P

26

SUBSTITUTE SHEET (RULE 26)

FIG. 8

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RSV F Expression in Chimeric Viruses

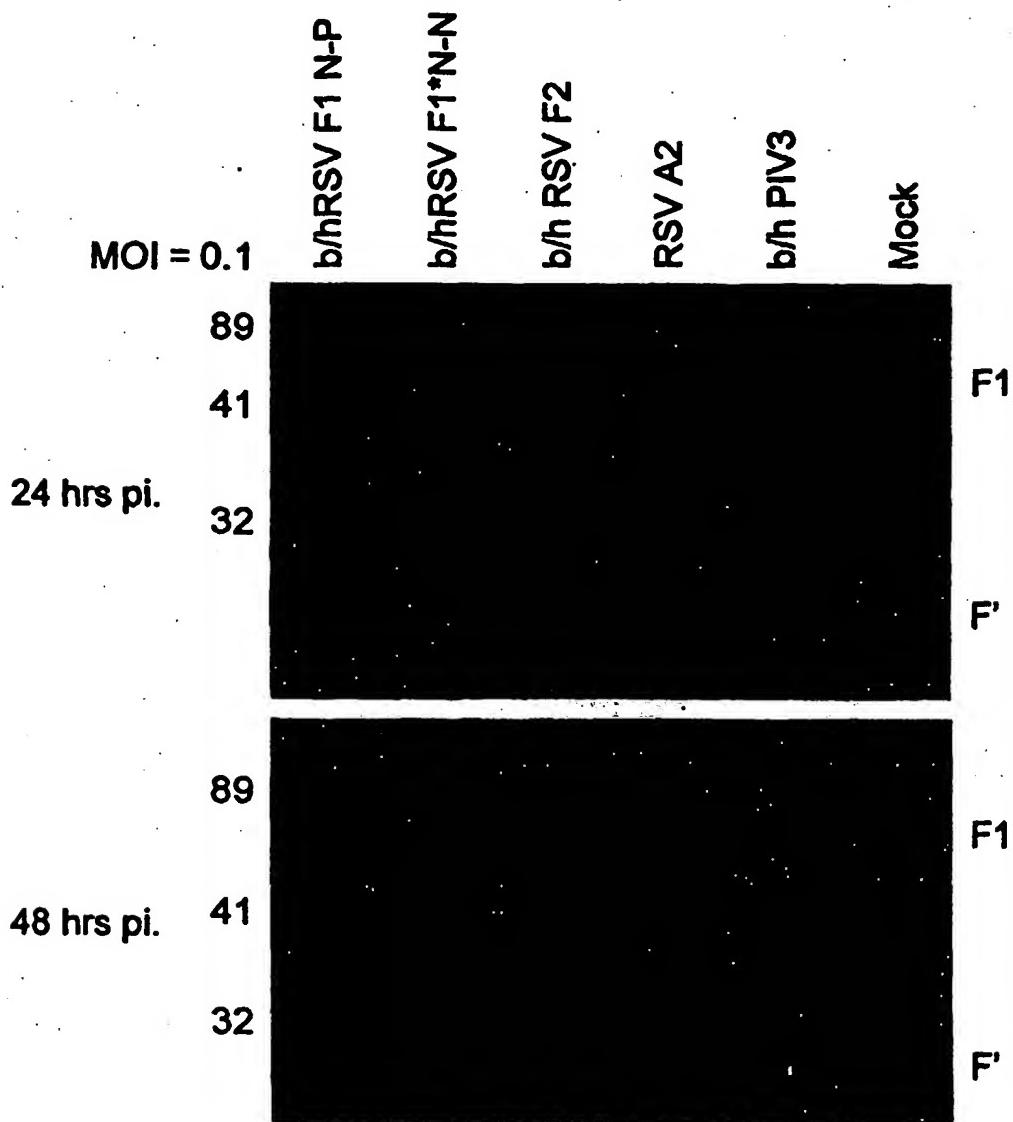


FIG.9(A)

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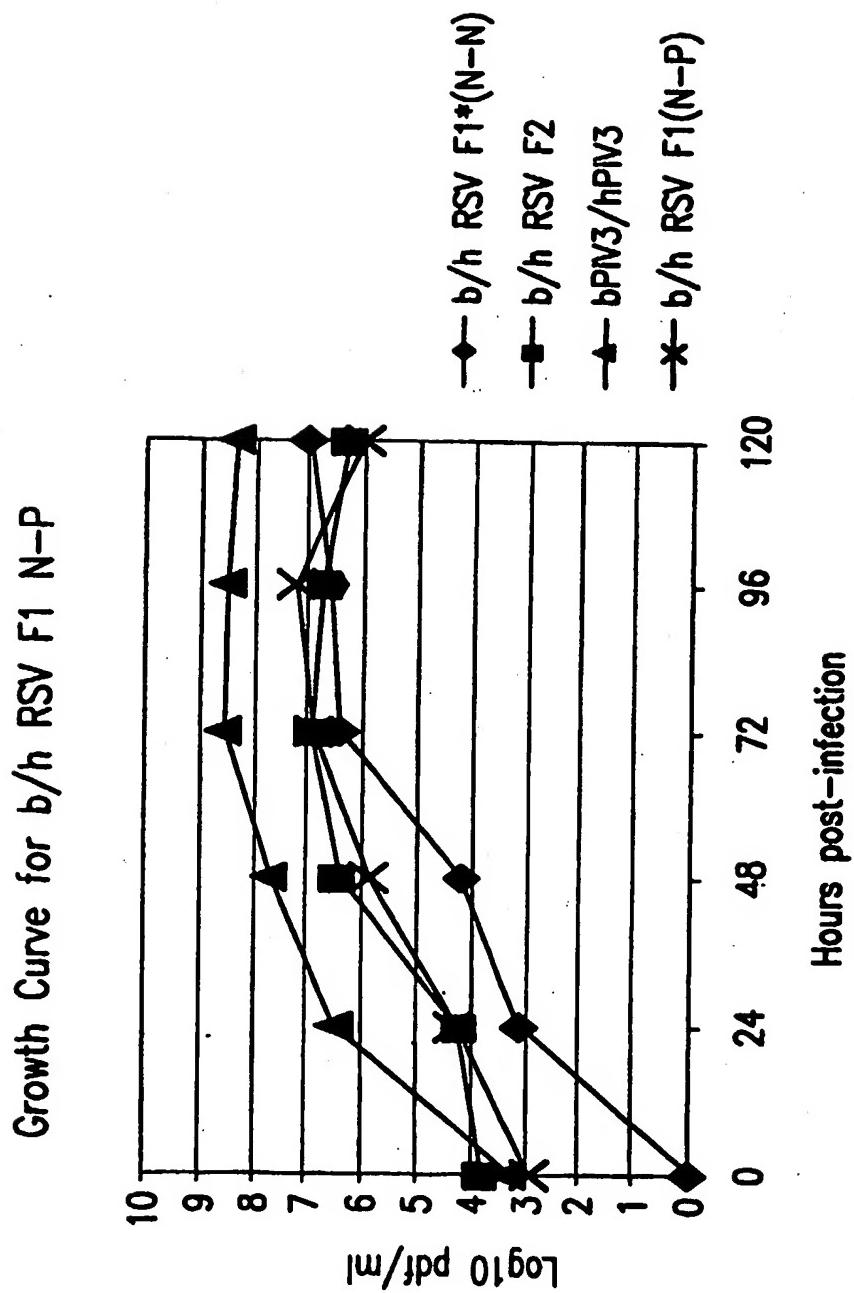
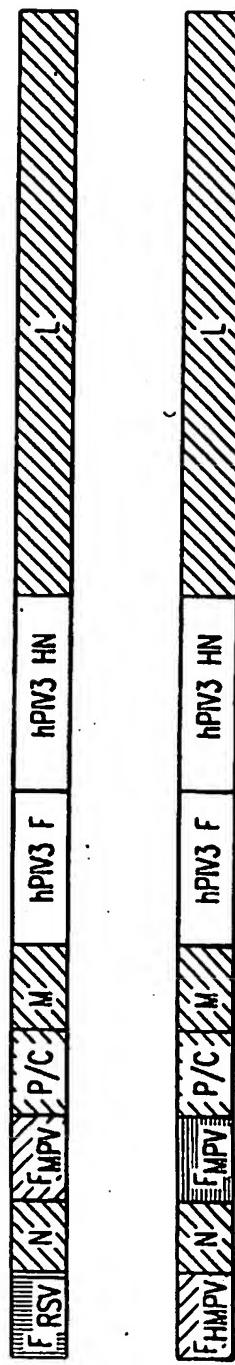


FIG. 9(B)

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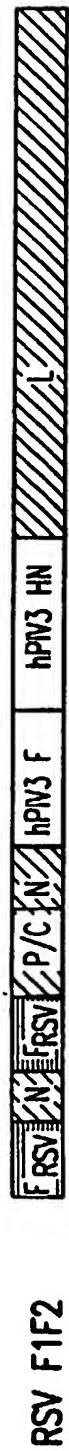
Trivalent bPIV3/hPIV3 vectored Constructs

Status: Constructs were rescued, viruses are being amplified in Vero cells.

FIG. 10

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Cloning of Two RSV F to the b/h PIV3 Vector



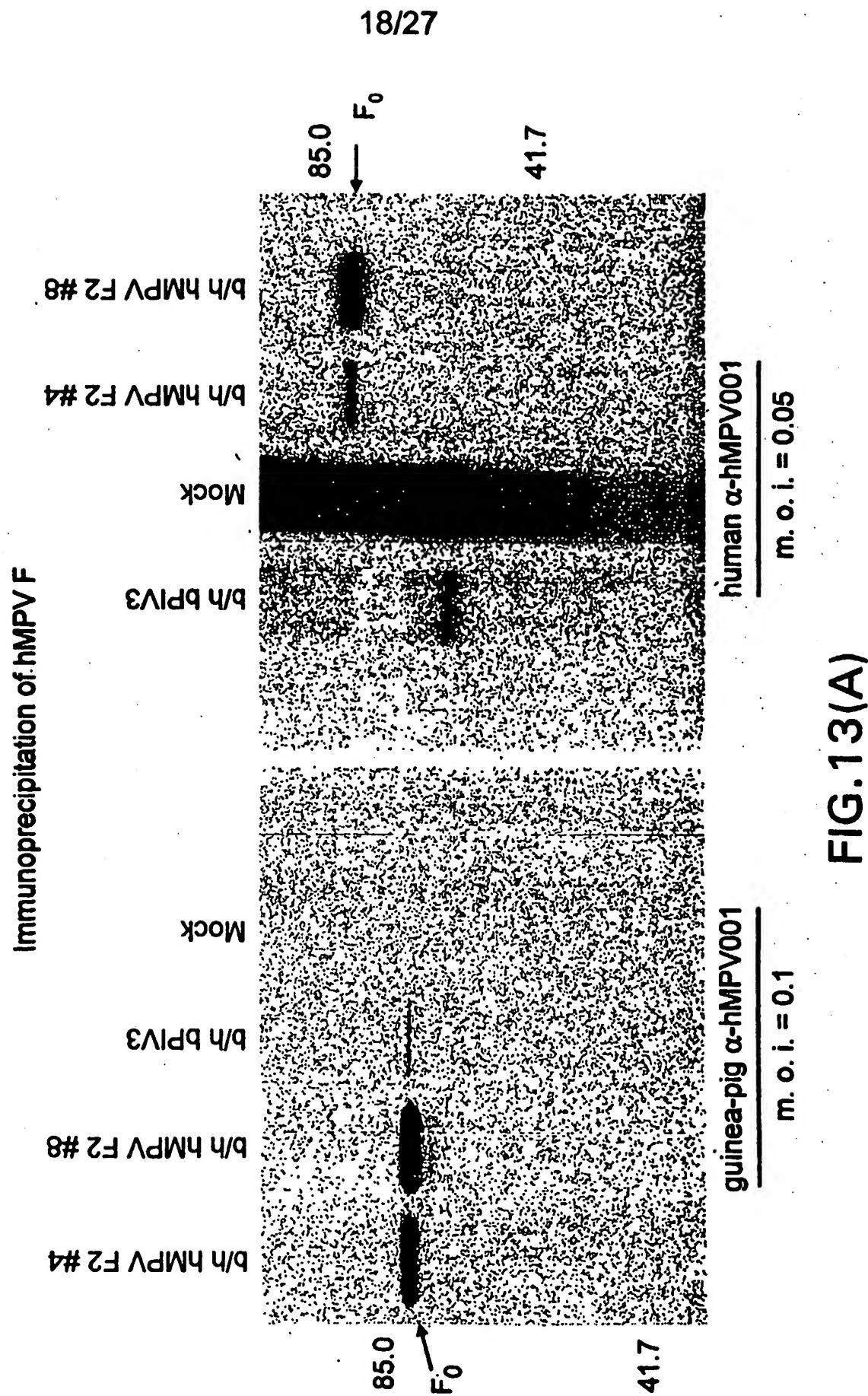
Status: Virus titer = 1.0×10^6 PFU/ml

Purpose: to study whether two RSV F genes will increase immunogenicity.

FIG. 11

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bPIV3/hPIV3 vectored hMPV F Constructs**1. b/h PIV3/hMPV F1****Status:** Virus stocks generated**Titer:** 5×10^6 PFU/ml**2. b/h PIV3/hMPV F2****Status:** Virus stock generated**Titer:** 1.5×10^7 PFU/ml**FIG. 12**



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Growth Curve of b/h PIV3/ hMPV F2 in Vero Cells,
MOI = 0.1

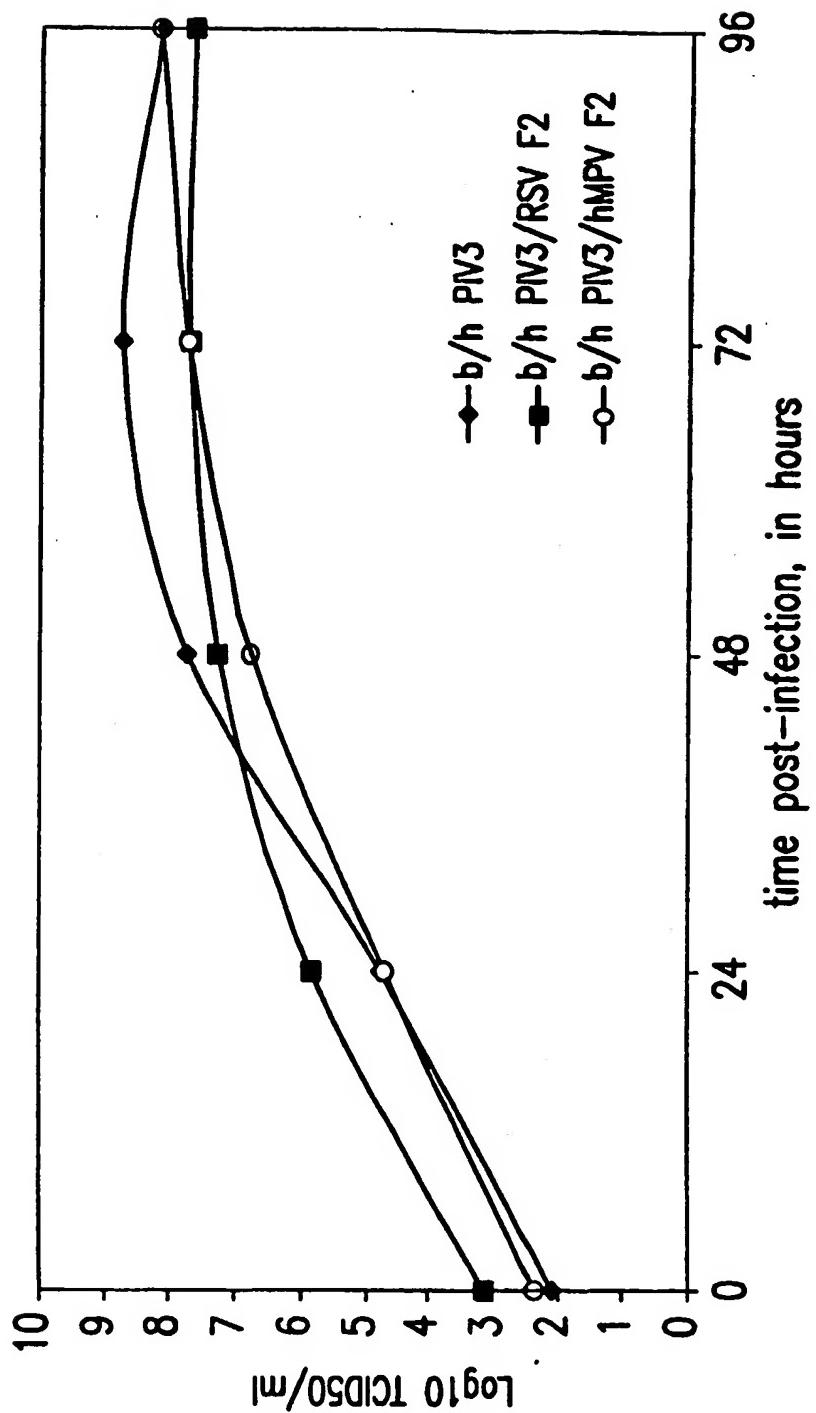


FIG. 13(B)

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Growth Curves of b/h PIV3/hMPV F1 and F2
in Vero Cells, MOI = 0.01

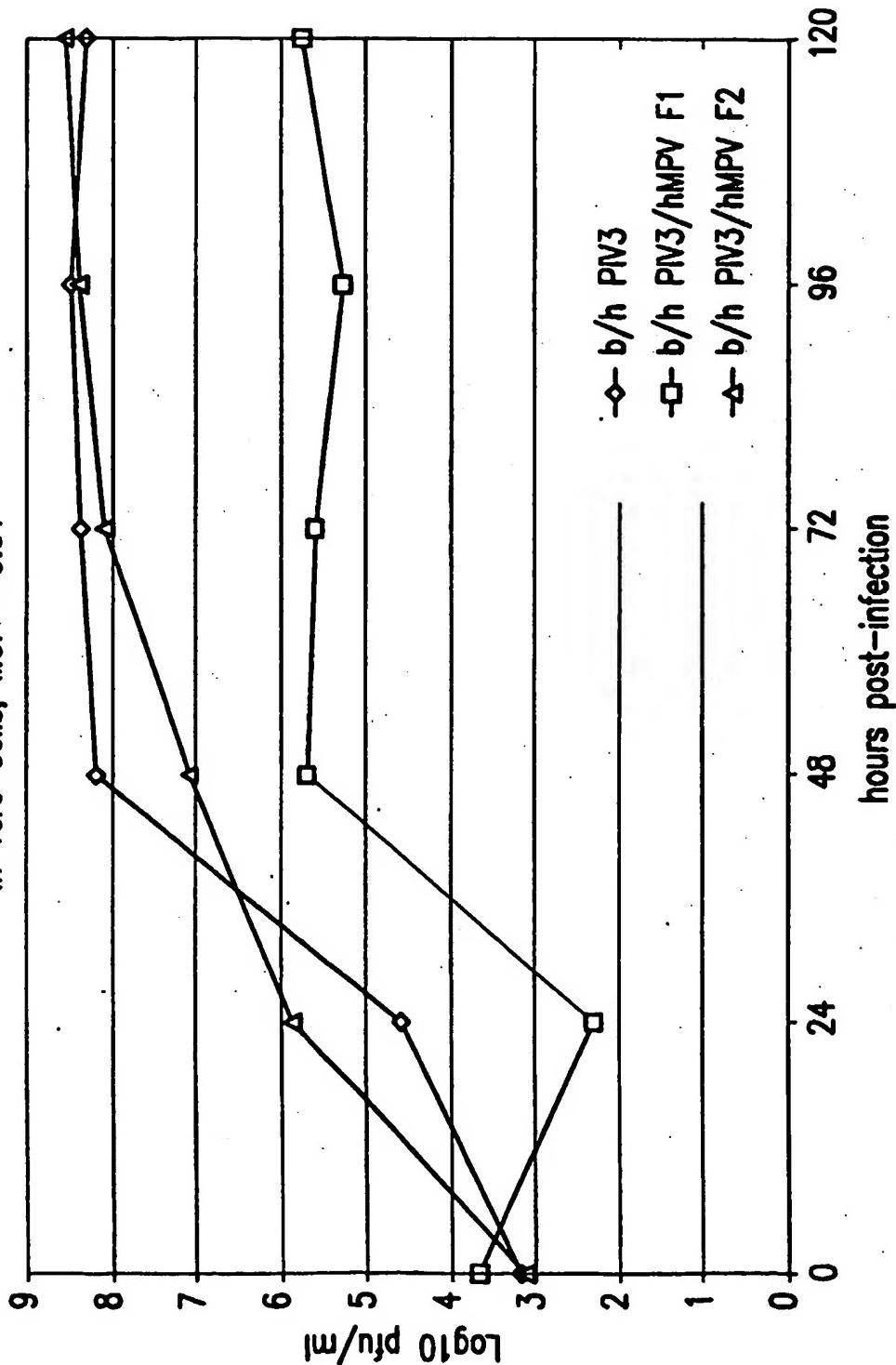
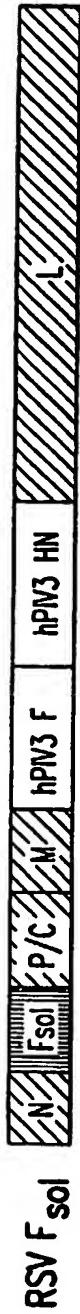


FIG. 13(C)

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Cloning of the Soluble RSV F Gene



Status: Full-length cDNA is being generated.
Purpose: to study whether a soluble RSV F protein without the trans-membrane and intracellular domains will be immunogenic.

FIG. 14

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b/h PIV3/hMPV F1

- liquid overlay on Vero cells
- limiting dilution from 10^{-2} to 10^{-7}
- immunostained with hMPV gp antiserum

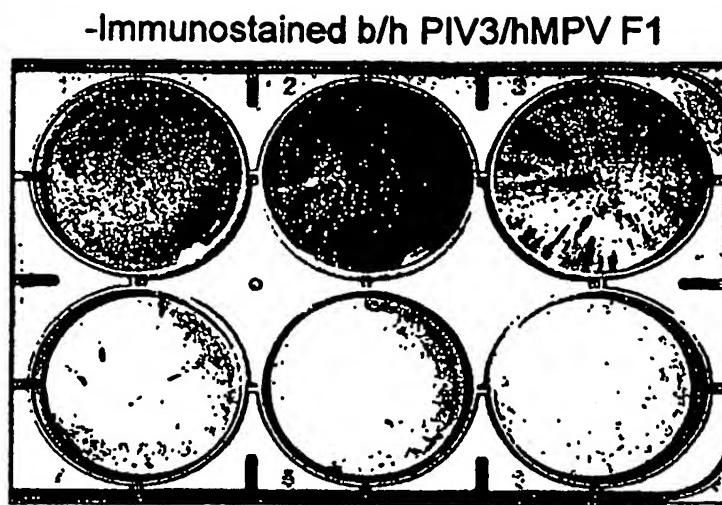


FIG.15(A)

-b/h PIV3/hMPV F2

- methyl cellulose overlay
- on Vero cells
- plaque assay from 10^{-2} to 10^{-7}
- immunostained with hMPV gp antiserum

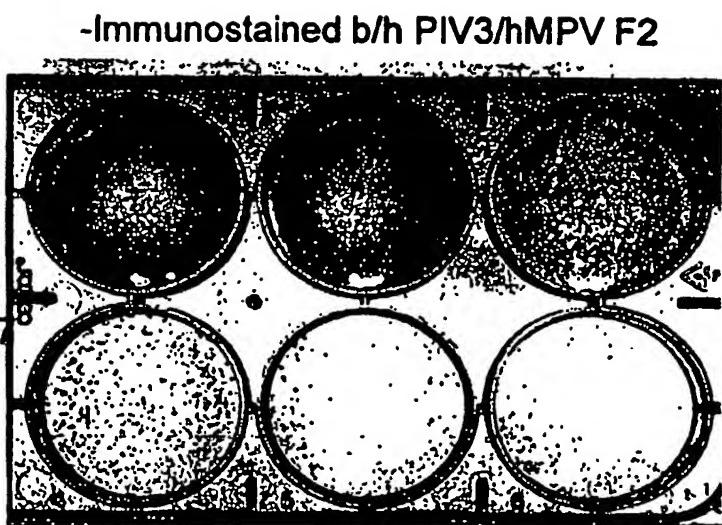


FIG.15(B)

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Free RSV F Protein in 20 - 66% Sucrose Gradient
(baculovirus expressed; C terminal truncation)

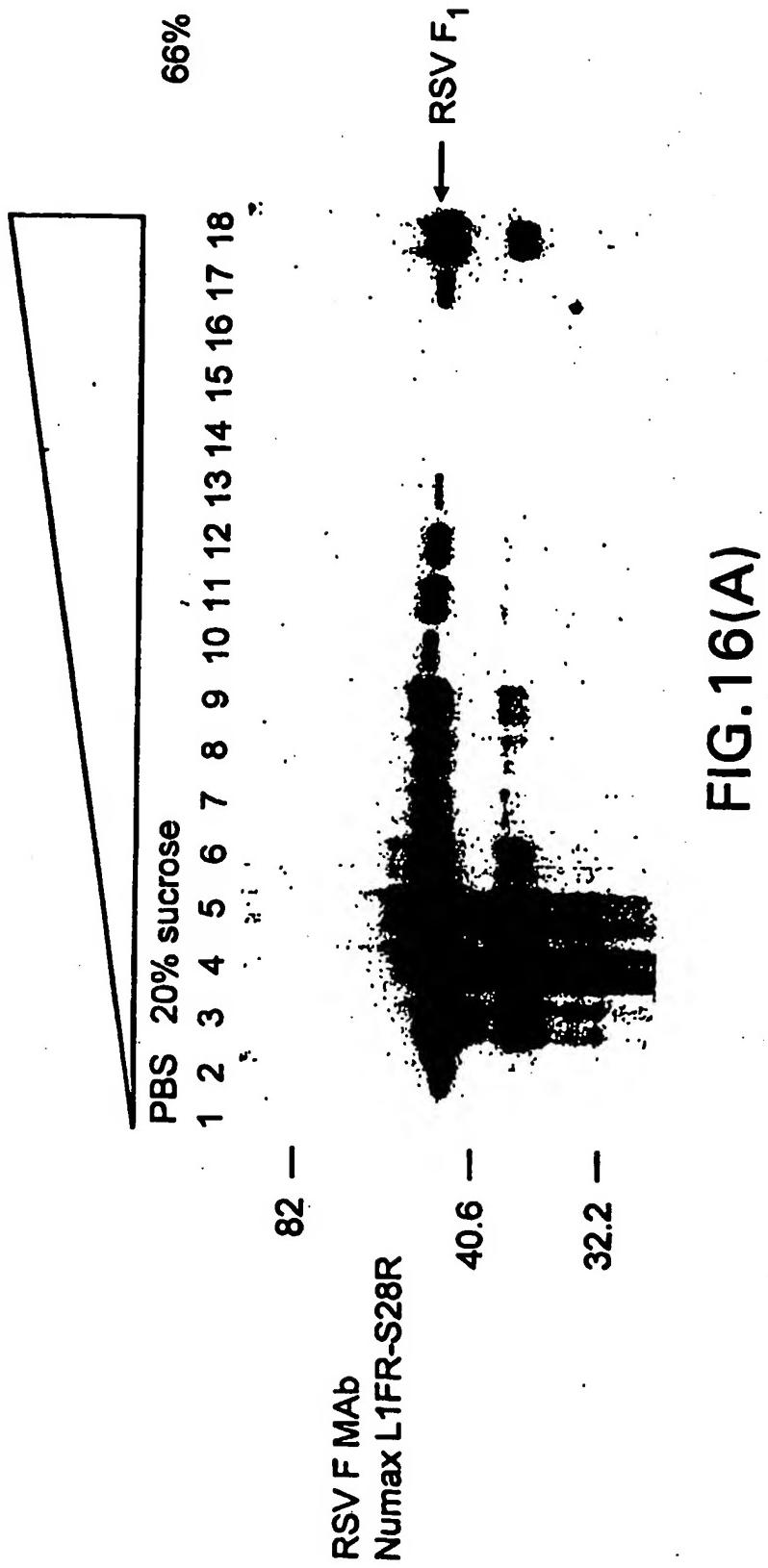


FIG. 16(A)

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**RSV Sucrose Gradient
(spun for 15 hrs @ 25,000 rpm)**

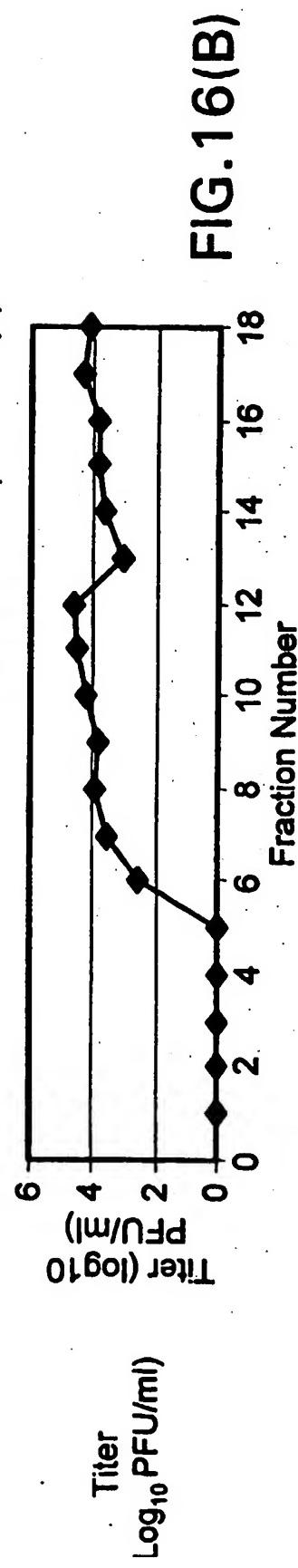
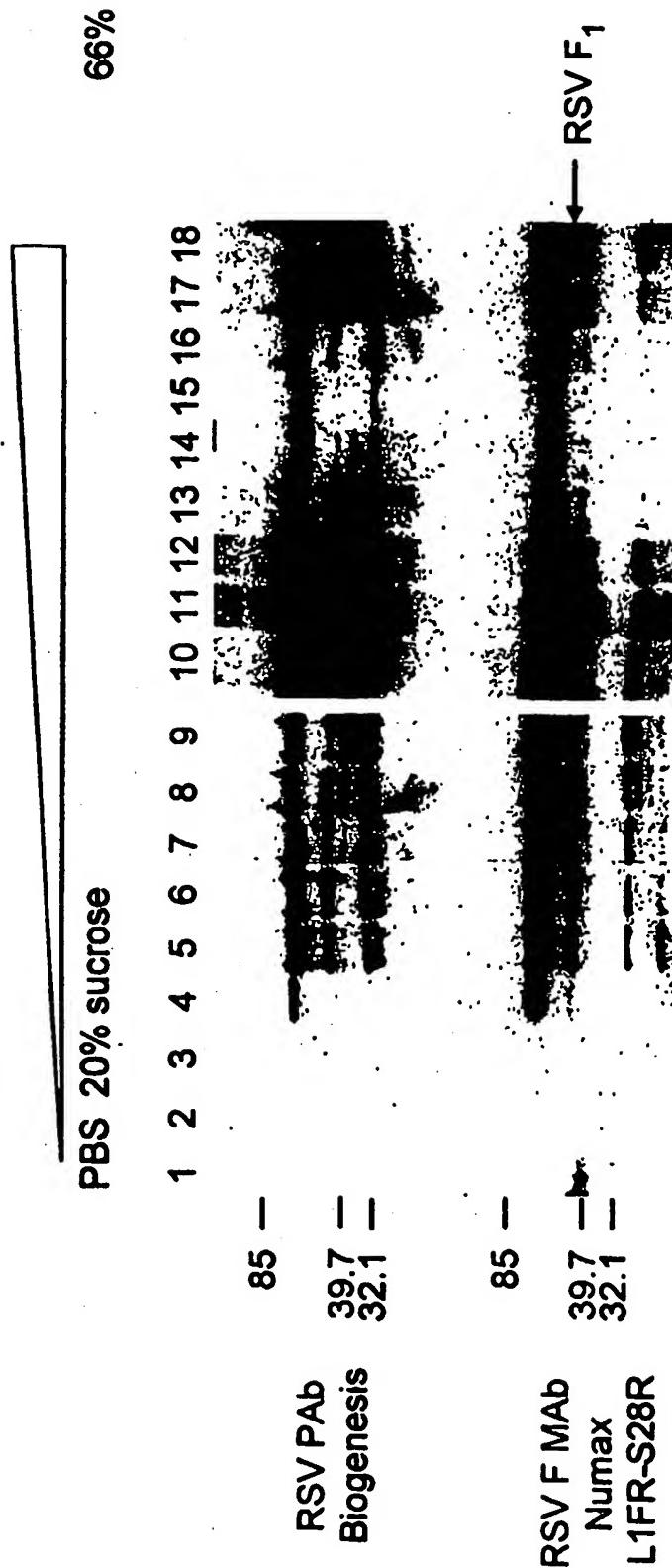


FIG. 16(B)

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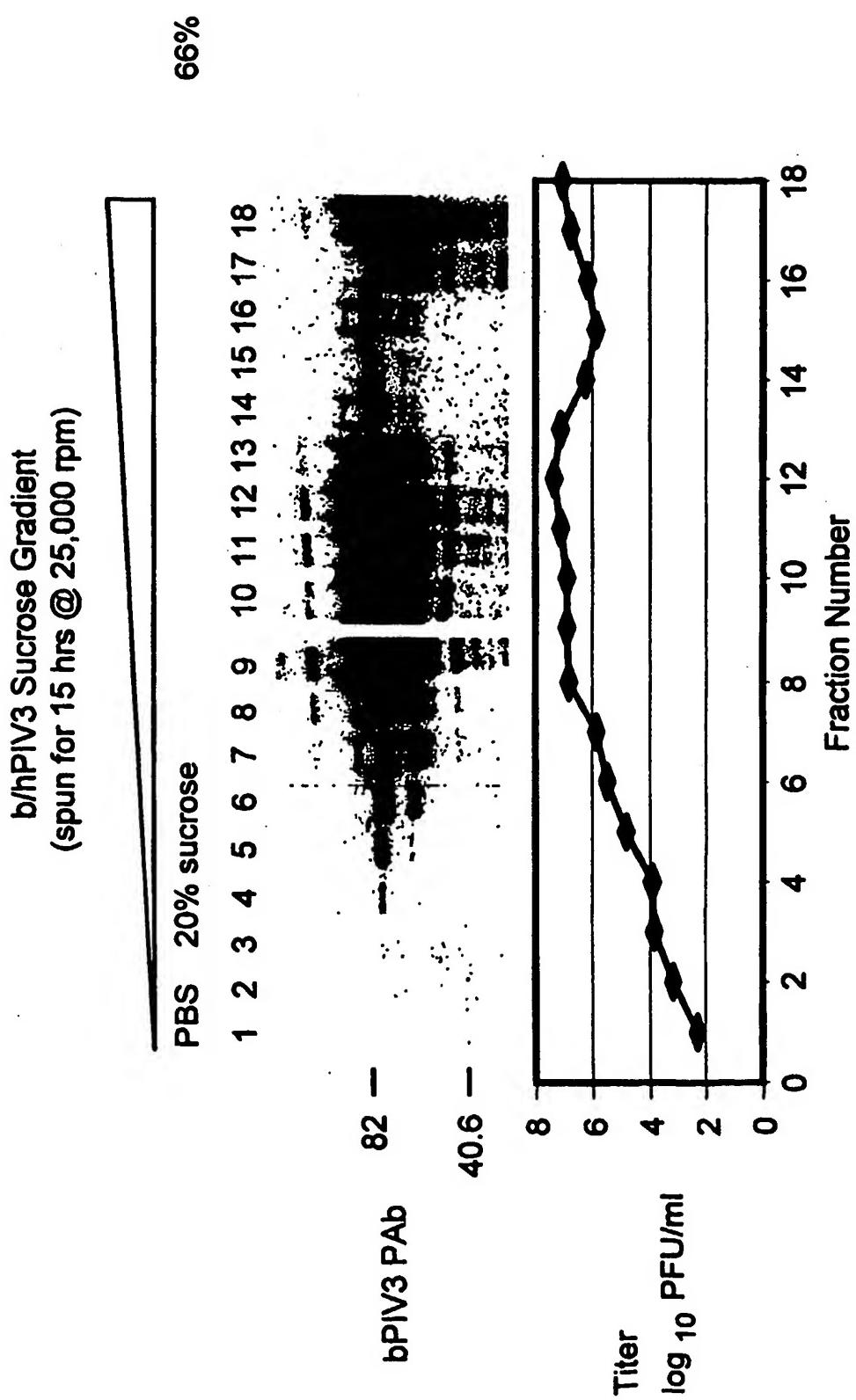
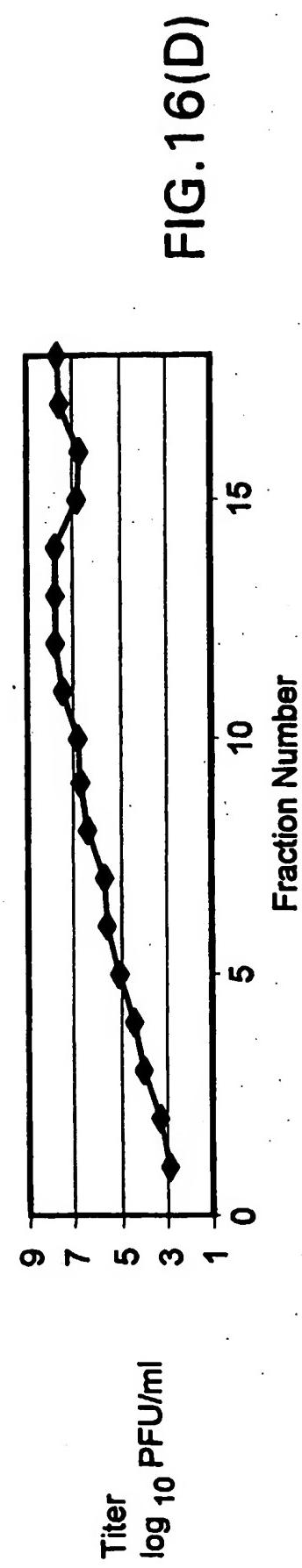
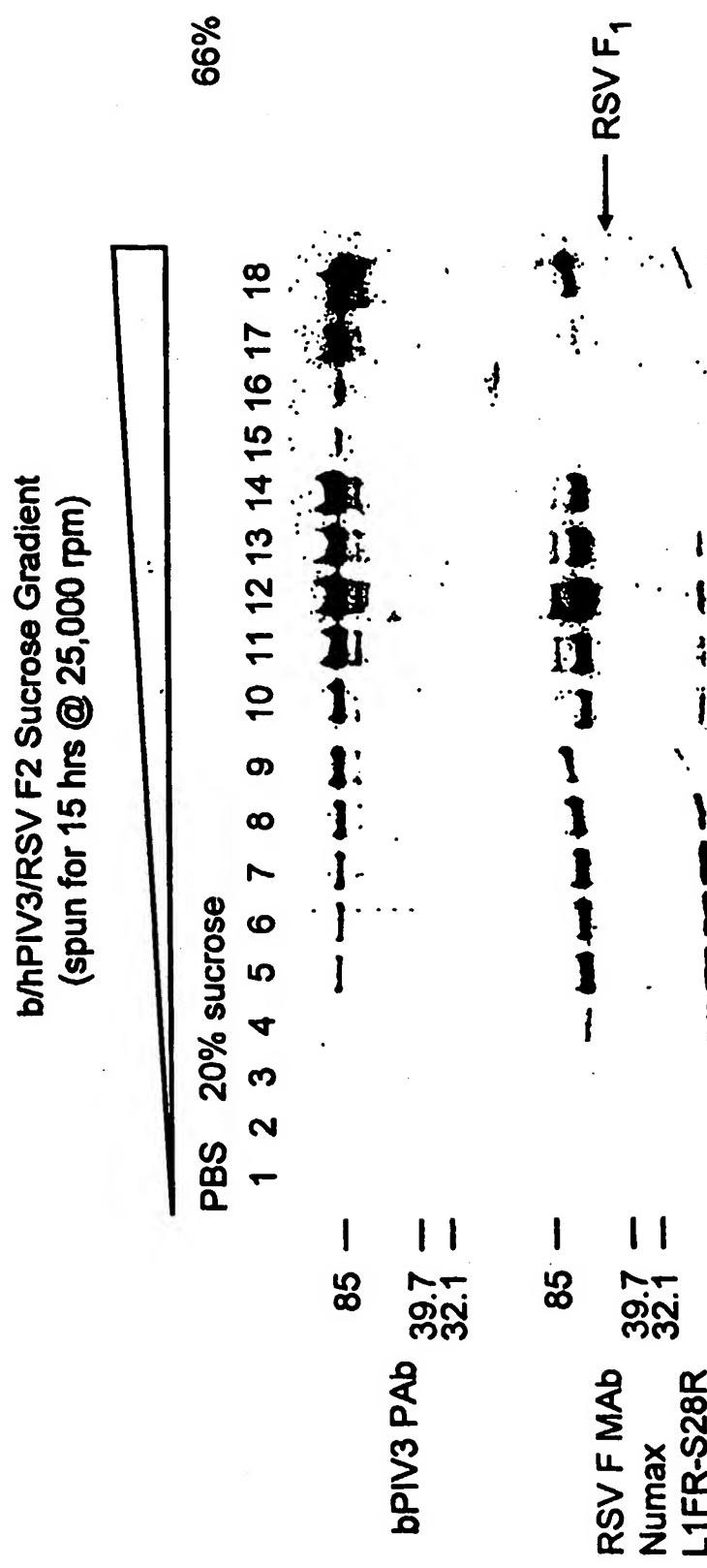


FIG. 16(C)

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**b/h PIV3/RSV G2 Sucrose Gradient
(spun for 15 hrs @ 25,000 rpm)**

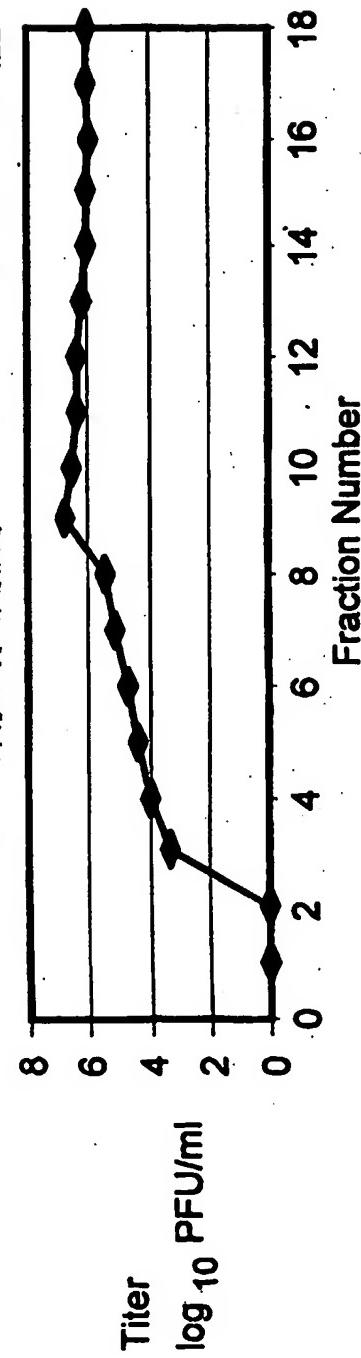
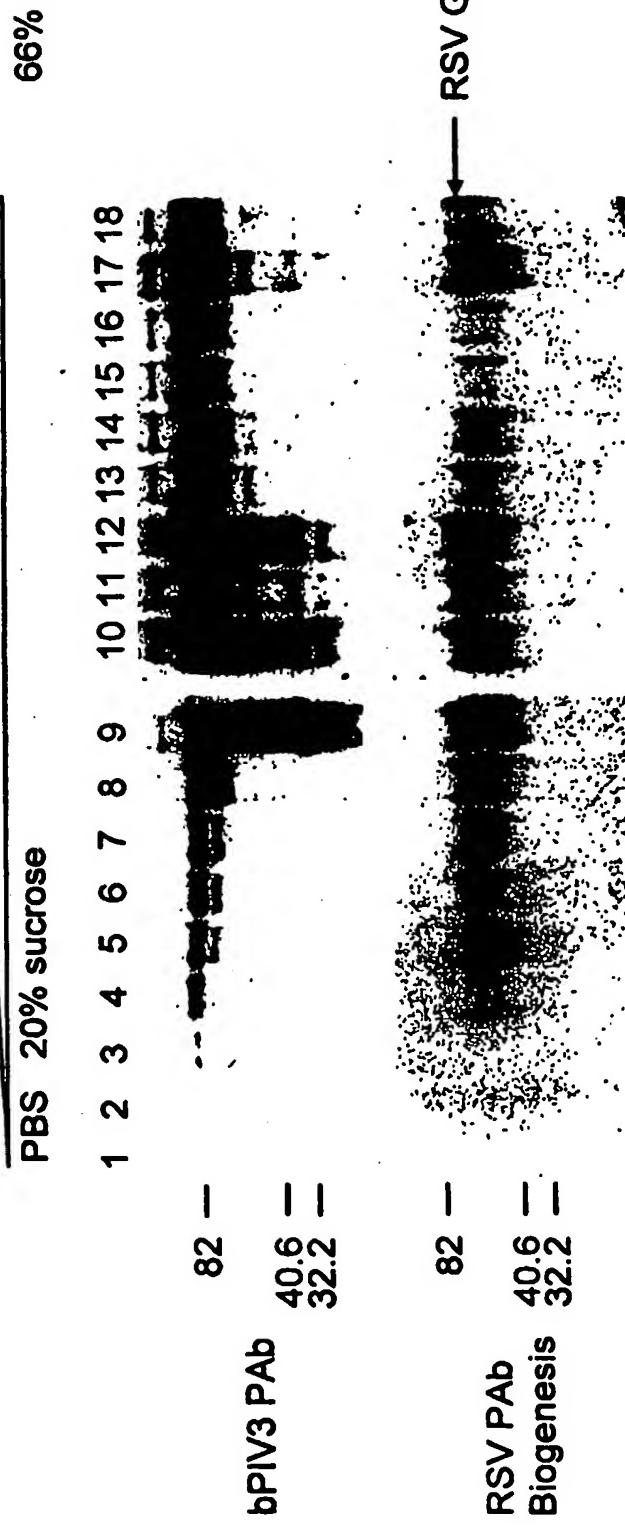


FIG. 16(E)

SEQUENCE LISTING

<110> MedImmune Vaccines, Inc.
ViroNovative BV

<120> RECOMBINANT PARAFLUENZA VIRUS
EXPRESSION SYSTEMS AND VACCINES
COMPRISING HETEROLOGOUS ANTIGENS
DERIVED FROM METAPNEUMOVIRUS

<130> 7682-061-228

<140> To be assigned
<141> Herewith

<150> 60/358,934
<151> 2002-02-21

<160> 327

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 2507
<212> DNA
<213> metapneumovirus

<220>
<221> CDS
<222> (1)...(2507)
<223> Human metapneumovirus isolate 00-1 matrix protein
· (M) and fusion protein (F) genes

<400> 1
atggagtctt accttagtaa cacctatcaa ggcattcctt acacagcagc tttcaagtt 60
gatctaatacg aaaaggaccc ttacactgca agcctaacaat tatggttccc ttgttttcag 120
gccaacacac caccacgt gctgctcgat cagctaaaaa ccctgacaat aaccactctg 180
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<211> 1596
<212> DNA
<213> pneumovirus

<220>
<221> CDS
<222> (1)...(1596)
<223> Avian pneumovirus fusion protein gene, partial cds

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<210> 3
<211> 1666
<212> DNA
<213> pneumovirus

<220>
<221> CDS

<222> (14)...(1627)

<223> Avian pneumovirus isolate 1b fusion protein mRNA,
complete cds

<400> 3

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<210> 4

<211> 1636

<212> DNA

<213> rhinotracheitis virus

<220>

<221> CDS

<222> (13)...(1629)

<223> Turkey rhinotracheitis virus gene for fusion
protein (F1 and F2 subunits), complete cds

<400> 4

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 <211> 1860
 <212> DNA
 <213> pneumovirus

<220>
 <221> CDS
 <222> (1)...(110)
 <223> Avian pneumovirus matrix protein (M) gene, partial
 cds

<220>
 <221> CDS
 <222> (216)...(1829)
 <223> Avian pneumovirus fusion glycoprotein (F) gene,
 complete cds

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<211> 574
<212> PRT
<213> paramyxovirus

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Tyr Gln Ser Thr Cys Ser Ala Val Ser Arg Gly Tyr Phe Ser Ala Leu
35 40 45
Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
50 55 60
Lys Glu Thr Lys Cys Asn Gly Thr Asp Thr Lys Val Lys Leu Ile Lys
65 70 75 80
Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
85 90 95
Met Gln Asn Thr Pro Ala Ala Asn Asn Arg Ala Arg Arg Glu Ala Pro
100 105 110
Gln Tyr Met Asn Tyr Thr Ile Asn Thr Thr Lys Asn Leu Asn Val Ser
115 120 125
Ile Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
130 135 140
Gly Ser Ala Ile Ala Ser Gly Ile Ala Val Ser Lys Val Leu His Leu
145 150 155 160
Glu Gly Glu Val Asn Lys Ile Lys Asn Ala Leu Leu Ser Thr Asn Lys
165 170 175
Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val
180 185 190
Leu Asp Leu Lys Asn Tyr Ile Asn Asn Gln Leu Leu Pro Ile Val Asn
195 200 205
Gln Gln Ser Cys Arg Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
210 215 220
Gln Lys Asn Ser Arg Leu Leu Glu Ile Asn Arg Glu Phe Ser Val Asn
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Ala Gly Val Thr Thr Pro Leu Ser Thr Tyr Met Leu Thr Asn Ser Glu
245 250 255
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260 265 270
Leu Met Ser Ser Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
275 280 285
Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro
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Ile Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro
305 310 315 320
Leu Cys Thr Thr Asn Ile Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg
325 330 335
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Pro Gln Ala Asp Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp
355 360 365
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370 375 380
Asp Ile Phe Asn Ser Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr
385 390 395 400
Asp Ile Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys
405 410 415
Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile
420 425 430
Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp

435

440

445

Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Leu Glu Gly
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 485 490 495
 Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Arg Ser Asp Glu Leu
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 Thr Ile Ile Ile Val Ile Ile Val Val Leu Leu Ser Leu Ile Ala Ile
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 Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile Ala Phe Ser Lys
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<210> 7
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 <212> PRT
 <213> paramyxovirus

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 Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
 50 55 60
 Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
 65 70 75 80
 Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
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 Met Gln Ser Thr Pro Pro Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro
 100 105 110
 Arg Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr
 115 120 125
 Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
 130 135 140
 Gly Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys Val Leu His Leu
 145 150 155 160
 Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys
 165 170 175
 Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val
 180 185 190
 Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn
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 Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
 210 215 220
 Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
 225 230 235 240
 Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu
 245 250 255
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 260 265 270
 Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
 275 280 285

Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro
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 305 310 315 320
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 Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe
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 485 490 495
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 <212> PRT
 <213> metapneumovirus

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 50 55 60
 Lys Ser Ala Leu Arg Glu Leu Arg Thr Val Ser Ala Asp Gln Leu Ala
 65 70 75 80
 Arg Glu Glu Gln Ile Glu Asn Pro Arg Gln Ser Arg Phe Val Leu Gly
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<211> 539
<212> PRT
<213> metapneumovirus

<400> 9
Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
1 5 10 15
His Gly Leu Lys Glu Ser Tyr Leu Glu Ser Cys Ser Thr Ile Thr
20 25 30
Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
35 40 45
Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ala Asp Gly Pro
50 55 60
Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
65 70 75 80
Leu Arg Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
85 90 95
Asn Pro Arg Gln Ser Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
100 105 110
Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
115 120 125
Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Lys Thr
130 135 140
Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
145 150 155 160
Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
165 170 175
Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
180 185 190
Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
195 200 205
Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
210 215 220
Ala Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln
225 230 235 240
Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
245 250 255
Gly Phe Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
260 265 270
Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
275 280 285
Ala Pro Ser Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
290 295 300
Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
305 310 315 320
Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
325 330 335
Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
340 345 350
Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
355 360 365
Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
370 375 380
Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
385 390 395 400
Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
405 410 415
Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
420 425 430
Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Phe Asp Pro
435 440 445

Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
 450 455 460
 Glu Ser Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
 465 470 475 480
 Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
 485 490 495
 Leu Ile Ala Val Leu Gly Ser Thr Met Ile Leu Val Ser Val Phe Ile
 500 505 510
 Ile Ile Lys Lys Thr Lys Arg Pro Thr Gly Ala Pro Pro Glu Leu Ser
 515 520 525
 Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
 530 535

<210> 10
<211> 532
<212> PRT
<213> Avian pneumovirus

<400> 10
Met Ser Trp Lys Val Val Leu Leu Leu Val Leu Ala Thr Pro Thr
 1 5 10 15
Gly Gly Leu Glu Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Val Thr
 20 25 30
Arg Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
 35 40 45
Thr Leu Gly Val Gly Asp Val Lys Asn Leu Thr Cys Thr Asp Gly Pro
 50 55 60
Ser Leu Ile Arg Thr Glu Leu Glu Leu Thr Lys Asn Ala Leu Glu Glu
 65 70 75 80
Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Lys Glu Ala Arg Ile Met
 85 90 95
Ser Pro Arg Lys Ala Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
 100 105 110
Ala Thr Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
 115 120 125
Arg Leu Glu Gly Glu Val Ala Ala Ile Lys Gly Ala Leu Arg Lys Thr
 130 135 140
Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
 145 150 155 160
Ala Val Asn Asp Leu Lys Asp Phe Ile Ser Lys Lys Leu Thr Pro Ala
 165 170 175
Ile Asn Arg Asn Lys Cys Asp Ile Ser Asp Leu Lys Met Ala Val Ser
 180 185 190
Phe Gly Gln Tyr Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
 195 200 205
Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
 210 215 220
Ala Glu Leu Val Arg Ala Val Ser Asn Met Pro Thr Ser Ser Gly Gln
 225 230 235 240
Ile Asn Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
 245 250 255
Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Val Tyr Ile Val Gln
 260 265 270
Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Arg Val Lys Ala
 275 280 285
Ala Pro Leu Cys Ser Gly Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg
 290 295 300
Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
 305 310 315 320
Pro Asn Glu Glu Asp Cys Glu Val Arg Ser Asp His Val Phe Cys Asp
 325 330 335

Thr Ala Ala Gly Ile Asn Val Ala Lys Glu Ser Glu Glu Cys Asn Arg
 340 345 350
 Asn Ile Ser Thr Thr Lys Tyr Pro Cys Lys Val Ser Thr Gly Arg His
 355 360 365
 Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
 370 375 380
 Tyr Asp Gly Met Ser Cys Ser Ile Gly Ser Asn Lys Val Gly Ile Ile
 385 390 395 400
 Arg Pro Leu Gly Lys Gly Cys Ser Tyr Ile Ser Asn Gln Asp Ala Asp
 405 410 415
 Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
 420 425 430
 Glu Gln His Thr Ile Lys Gly Lys Pro Val Ser Ser Asn Phe Asp Pro
 435 440 445
 Ile Glu Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
 450 455 460
 Glu Ser Val Glu Lys Ser Gln Asn Leu Ile Asp Gln Ser Asn Lys Ile
 465 470 475 480
 Leu Asp Ser Ile Glu Lys Gly Asn Ala Gly Phe Val Ile Val Ile Val
 485 490 495
 Leu Ile Val Leu Leu Met Leu Ala Ala Val Gly Val Gly Val Phe Phe
 500 505 510
 Val Val Lys Lys Arg Lys Ala Ala Pro Lys Phe Pro Met Glu Met Asn
 515 520 525
 Gly Val Asn Asn
 530

<210> 11
 <211> 537
 <212> PRT
 <213> Avian pneumovirus

<400> 11
 Met Ser Trp Lys Val Val Leu Leu Leu Val Leu Ala Thr Pro Thr
 1 5 10 15
 Gly Gly Leu Glu Glu Ser Tyr Leu Glu Ser Cys Ser Thr Val Thr
 20 25 30
 Arg Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
 35 40 45
 Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
 50 55 60
 Ser Leu Ile Arg Thr Glu Leu Glu Leu Thr Lys Asn Ala Leu Glu Glu
 65 70 75 80
 Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Lys Glu Ala Arg Ile Met
 85 90 95
 Ser Pro Arg Lys Ala Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
 100 105 110
 Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
 115 120 125
 Arg Leu Glu Gly Glu Val Ala Ala Ile Lys Gly Ala Leu Arg Lys Thr
 130 135 140
 Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
 145 150 155 160
 Ala Val Asn Asp Leu Lys Asp Phe Ile Ser Lys Lys Leu Thr Pro Ala
 165 170 175
 Ile Asn Arg Asn Lys Cys Asp Ile Ser Asp Leu Lys Met Ala Val Ser
 180 185 190
 Phe Gly Gln Tyr Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
 195 200 205
 Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
 210 215 220

Ala Glu Leu Val Arg Ala Val Ser Asn Met Pro Thr Ser Ser Gly Gln
 225 230 235 240
 Ile Asn Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
 245 250 255
 Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Val Tyr Ile Val Gln
 260 265 270
 Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Lys Val Lys Ala
 275 280 285
 Ala Pro Leu Cys Ser Gly Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg
 290 295 300
 Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
 305 310 315 320
 Pro Asn Glu Glu Asp Cys Glu Val Arg Ser Asp His Val Phe Cys Asp
 325 330 335
 Thr Ala Ala Gly Ile Asn Val Ala Lys Glu Ser Glu Glu Cys Asn Arg
 340 345 350
 Asn Ile Ser Thr Thr Lys Tyr Pro Cys Lys Val Ser Thr Gly Arg His
 355 360 365
 Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
 370 375 380
 Tyr Asp Gly Met Ser Cys Ser Ile Gly Ser Asn Lys Val Gly Ile Ile
 385 390 395 400
 Arg Pro Leu Gly Lys Gly Cys Ser Tyr Ile Ser Asn Gln Asp Ala Asp
 405 410 415
 Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
 420 425 430
 Glu Gln His Thr Ile Lys Gly Lys Pro Val Ser Ser Asn Phe Asp Pro
 435 440 445
 Ile Glu Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
 450 455 460
 Glu Ser Val Glu Lys Ser Gln Asn Leu Ile Asp Gln Ser Asn Lys Ile
 465 470 475 480
 Leu Asp Ser Ile Glu Lys Gly Asn Ala Gly Phe Val Ile Val Ile Val
 485 490 495
 Leu Ile Val Leu Met Leu Ala Ala Val Gly Val Gly Val Phe Phe
 500 505 510
 Val Val Lys Lys Arg Lys Ala Ala Pro Lys Phe Pro Met Glu Met Asn
 515 520 525
 Gly Val Asn Asn Lys Gly Phe Ile Pro
 530 535

<210> 12
 <211> 538
 <212> PRT
 <213> Turkey rhinotracheitis virus

<400> 12
 Met Asp Val Arg Ile Cys Leu Leu Phe Leu Ile Ser Asn Pro Ser
 1 5 10 15
 Ser Cys Ile Gln Glu Thr Tyr Asn Glu Glu Ser Cys Ser Thr Val Thr
 20 25 30
 Arg Gly Tyr Lys Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
 35 40 45
 Asn Leu Glu Ile Gly Asn Val Glu Asn Ile Thr Cys Asn Asp Gly Pro
 50 55 60
 Ser Leu Ile Asp Thr Glu Leu Val Leu Thr Lys Asn Ala Leu Arg Glu
 65 70 75 80
 Leu Lys Thr Val Ser Ala Asp Gln Val Ala Lys Glu Ser Arg Leu Ser
 85 90 95
 Ser Pro Arg Arg Arg Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
 100 105 110

Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Leu Ala Lys Thr Ile
 115 120 125
 Arg Leu Glu Gly Glu Val Lys Ala Ile Lys Asn Ala Leu Arg Asn Thr
 130 135 140
 Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
 145 150 155 160
 Ala Val Asn Asp Leu Lys Glu Phe Ile Ser Lys Lys Leu Thr Pro Ala
 165 170 175
 Ile Asn Gln Asn Lys Cys Asn Ile Ala Asp Ile Lys Met Ala Ile Ser
 180 185 190
 Phe Gly Gln Asn Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
 195 200 205
 Asp Ser Ala Gly Ile Thr Ser Ala Val Ser Leu Asp Leu Met Thr Asp
 210 215 220
 Asp Glu Leu Val Arg Ala Ile Asn Arg Met Pro Thr Ser Ser Gly Gln
 225 230 235 240
 Ile Ser Leu Met Leu Asn Asn Arg Ala Met Val Arg Arg Lys Gly Phe
 245 250 255
 Gly Ile Leu Ile Gly Val Tyr Asp Gly Thr Val Val Tyr Met Val Gln
 260 265 270
 Leu Pro Ile Phe Gly Val Ile Glu Thr Pro Cys Trp Arg Val Val Ala
 275 280 285
 Ala Pro Leu Cys Arg Lys Glu Lys Gly Asn Tyr Ala Cys Ile Leu Arg
 290 295 300
 Glu Asp Gln Gly Trp Tyr Cys Thr Asn Ala Gly Ser Thr Ala Tyr Tyr
 305 310 315 320
 Pro Asn Lys Asp Asp Cys Glu Val Arg Asp Asp Tyr Val Phe Cys Asp
 325 330 335
 Thr Ala Ala Gly Ile Asn Val Ala Leu Glu Val Glu Gln Cys Asn Tyr
 340 345 350
 Asn Ile Ser Thr Ser Lys Tyr Pro Cys Lys Val Ser Thr Gly Arg His
 355 360 365
 Pro Val Ser Met Val Ala Leu Thr Pro Leu Gly Gly Leu Val Ser Cys
 370 375 380
 Tyr Glu Ser Val Ser Cys Ser Ile Gly Ser Asn Lys Val Gly Ile Ile
 385 390 395 400
 Lys Gln Leu Gly Lys Gly Cys Thr His Ile Pro Asn Asn Glu Ala Asp
 405 410 415
 Thr Ile Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Val Gly
 420 425 430
 Glu Gln Arg Thr Ile Lys Gly Ala Pro Val Val Asn Asn Phe Asn Pro
 435 440 445
 Ile Leu Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
 450 455 460
 Glu Ser Ile Asp Arg Ser Gln Asp Leu Ile Asp Lys Ser Asn Asp Leu
 465 470 475 480
 Leu Gly Ala Asp Ala Lys Ser Lys Ala Gly Ile Ala Ile Ala Ile Val
 485 490 495
 Val Leu Val Ile Leu Gly Ile Phe Phe Leu Leu Ala Val Ile Tyr Tyr
 500 505 510
 Cys Ser Arg Val Arg Lys Thr Lys Pro Lys His Asp Tyr Pro Ala Thr
 515 520 525
 Thr Gly His Ser Ser Met Ala Tyr Val Ser
 530 535

<210> 13
 <211> 537
 <212> PRT
 <213> Avian penumovirus

<400> 13

Met Ser Trp Lys Val Val Leu Leu Leu Val Leu Leu Ala Thr Pro Thr
 1 5 10 15
 Gly Gly Leu Glu Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Val Thr
 20 25 30
 Arg Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
 35 40 45
 Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
 50 55 60
 Ser Leu Ile Arg Thr Glu Leu Glu Leu Thr Lys Asn Ala Leu Glu Glu
 65 70 75 80
 Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Lys Glu Ala Arg Ile Met
 85 90 95
 Ser Pro Arg Lys Ala Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
 100 105 110
 Ala Thr Ala Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
 115 120 125
 Arg Leu Glu Gly Glu Val Ala Ala Ile Lys Gly Ala Leu Arg Lys Thr
 130 135 140
 Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
 145 150 155 160
 Ala Val Asn Asp Leu Lys Asp Phe Ile Ser Lys Lys Leu Thr Pro Ala
 165 170 175
 Ile Asn Arg Asn Lys Cys Asp Ile Ser Asp Leu Lys Met Ala Val Ser
 180 185 190
 Phe Gly Gln Tyr Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
 195 200 205
 Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
 210 215 220
 Ala Glu Leu Val Arg Ala Val Ser Asn Met Pro Thr Ser Ser Gly Gln
 225 230 235 240
 Ile Asn Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
 245 250 255
 Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Val Tyr Ile Val Gln
 260 265 270
 Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Lys Val Lys Ala
 275 280 285
 Ala Pro Leu Cys Ser Gly Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg
 290 295 300
 Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
 305 310 315 320
 Pro Asn Glu Glu Asp Cys Glu Val Arg Ser Asp His Val Phe Cys Asp
 325 330 335
 Thr Ala Ala Gly Ile Asn Val Ala Lys Glu Ser Glu Glu Cys Asn Arg
 340 345 350
 Asn Ile Ser Thr Thr Lys Tyr Pro Cys Lys Val Ser Thr Gly Arg His
 355 360 365
 Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
 370 375 380
 Tyr Asp Gly Met Ser Cys Ser Ile Gly Ser Asn Lys Val Gly Ile Ile
 385 390 395 400
 Arg Pro Leu Gly Lys Gly Cys Ser Tyr Ile Ser Asn Gln Asp Ala Asp
 405 410 415
 Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
 420 425 430
 Glu Gln His Thr Ile Lys Gly Lys Pro Val Ser Ser Asn Phe Asp Pro
 435 440 445
 Ile Glu Phe Pro Glu Asp Gln Phe Asn Ile Ala Leu Asp Gln Val Phe
 450 455 460
 Glu Ser Val Glu Lys Ser Gln Asn Leu Ile Asp Gln Ser Asn Lys Ile
 465 470 475 480
 Leu Asp Ser Ile Glu Lys Gly Asn Ala Gly Phe Val Ile Val Ile Val
 485 490 495

Leu Ile Val Leu Leu Met Leu Ala Ala Val Gly Val Gly Val Phe Phe
 500 505 510
 Val Val Lys Lys Arg Lys Ala Ala Pro Lys Phe Pro Met Glu Met Asn
 515 520 525
 Gly Val Asn Asn Lys Gly Phe Ile Pro
 530 535

<210> 14
<211> 1193
<212> DNA
<213> rhinotracheitis virus

<220>
<221> CDS
<222> (16)...(1191)
<223> Turkey rhinotracheitis virus (strain CVL14/1)
attachment protein (G) mRNA, complete cds

<400> 14
gggacaagta tctctatgggtc gtcacaaactatatggctc agggcaccagg tgcatatcaa 60
actgcagtgg ggttctggctt ggacatcggtt aggaggtaca tattggctat agtccttatca 120
gcttcgggc tgacactgcac agtcaactattt gcaactcaactg tttagcgtcat agttgaacag 180
tcagtgttagt aggagtgcag aaactacaat ggaggagata gagattgggtg gtcacaccacc 240
caggagcagc caactactgc accaagtgcg actccagcag gaaattatgg aggattacaa 300
acggctcgaa caagaaatgc tgaaagctgtt ttgcatgtca aaatttctta tggtgatatg 360
tatagccgca gtgatactgtt actgggttgtt tttgattgtt tgggttattt ggttctttgc 420
aaatcaggagc caatttgcgatc gcgagataat caagttgacc caacagccct ctgccattgc 480
agggttagatc tttcaagtgtt ggactgctgc aaggtgaaca agattagcac taacagcagc 540
accacctctg agccccagaa gaccaaccccg gcatggcccta gccaagacaa cacagactcc 600
gatccaaatc cccaaaggcat aaccaccaggc acagccactc tgctctcaac aagtctgggc 660
ctcatgctca catcgaagac tgggacacac aaatcagggc ccccccggc cttggccgggg 720
agcaacacca acggaaaaaac aaccacagac cgagaaccag gggccacaaa ccaacccaaat 780
tcaaccacca atgggcaaca caataaaacac acccaacgaa tgacacccccc gccaagtac 840
gacaacaccaaa gaaccatcctt ccagcacaca acaccctggg aaaagacatt cagtagatatac 900
aagcccacac actctccgac caacgaatca gatcaatccc tccccacaac tcaaaaacagc 960
atcaactgtt aacattttgtt ccccccggc aaggaaaaaaaaa tctgctacag agtaggttct 1020
tacaactcca atattacaaa gcaatgcaga attgatgttc ctttgtgttc cacttatagc 1080
acagtgtgca tgaaaacata ctataccgaa ccattcaact gttggaggcg tatctggcgt 1140
tgcttgcgtt atgacggagt tggctgtt gagggtgtt gcaactgtt actt 1193

<210> 15
<211> 1260
<212> DNA
<213> rhinotracheitis virus

<220>
<221> CDS
<222> (16)...(1260)
<223> Turkey rhinotracheitis virus (strain 6574)
attachment protein (G), complete cds

<400> 15
gggacaagta tccagatgggtc gtcagagctc tacatcatag aggggggttagtgc ctcatctgaa 60
atagtccatca agcaagtccatc cagaaggagc caaaaaatac tggtaggact ggtgttatca 120
gccttaggtt tgacactgcac tagcaactattt gtttatctt tttgttattt tagaagacag 180
gtcaaaattac gacagtgtgtt ggacacttattt tggggggaaa atggatccctt acatccaggg 240
cagtcacacag aaaatacttc aacaagaggtaa aagactacaa caaaagaccc tagaagatta 300
caggcgactg gaggcaggaaa gtttggagac tgggggtatgtt tgcaaggatgtt tgatgggtat 360
atgcatgtatc gcaggatgtatc tggactgtgtt ggtgttgcattt gtttgggtt atggctctt 420
tgtgaatcag gaccaattttt tcaggaggat acttgggtctg aagacggaaa cttctgcccga 480
tgcactttt cttccatgg ggtgagttgc tgcaaaaaaac ccaaaagacaa ggcaaccact 540

gcccagagga actccaaacc agctaacagc aaatcaactc ctccggtaca ttcagacagg 600
 gccagcaaag aacataatcc ctccccaggg gagcaacccc gcagggggcc aaccagcgc 660
 aagacaacta ttgcttagcac cccttcaaca gaggacactg ctaaaccac gattagcaaa 720
 cctaaactca ccatcaggcc ctgc当地aaga ggtccatccg gcagcacaaa agcagcctcc 780
 agcaccccca gccacaagac caacaccaga ggcaccagca agacgaccga ccagagaccc 840
 cgccaccggac ccactcccg aaggcccaga caaaccaca gcacagcaac tccgcccccc 900
 acaaccccaa tccacaaggg ccgggccccca acccccaaac caacaacaga cctcaaggtc 960
 aacccaaggg aaggcagcac aagcccaact gcaatacaga aaaacccaaac cacacaaagt 1020
 aatcttggtg actgcacact gtctgatcca gatgagccac aaaggattt tgaccaggt 1080
 ggaacttaca atcctagtca atcgggaacc tgcaacatag agttccaaa atgttccact 1140
 tatgggcatg cttgtatggc tacattatat gacacccat tcaactgctg gcgaggacc 1200
 aggagatgca tctgtgattc cggaggggag ctgattgagt ggtgctgtac tagtcaataa 1260

<210> 16
 <211> 391
 <212> PRT
 <213> Turkey rhinotracheitis virus

<400> 16
 Met Gly Ser Lys Leu Tyr Met Ala Gln Gly Thr Ser Ala Tyr Gln Thr
 1 5 10 15
 Ala Val Gly Phe Trp Leu Asp Ile Gly Arg Arg Tyr Ile Leu Ala Ile
 20 25 30
 Val Leu Ser Ala Phe Gly Leu Thr Cys Thr Val Thr Ile Ala Leu Thr
 35 40 45
 Val Ser Val Ile Val Glu Gln Ser Val Leu Glu Glu Cys Arg Asn Tyr
 50 55 60
 Asn Gly Gly Asp Arg Asp Trp Trp Ser Thr Thr Gln Glu Gln Pro Thr
 65 70 75 80
 Thr Ala Pro Ser Ala Thr Pro Ala Gly Asn Tyr Gly Gly Leu Gln Thr
 85 90 95
 Ala Arg Thr Arg Lys Ser Glu Ser Cys Leu His Val Gln Ile Ser Tyr
 100 105 110
 Gly Asp Met Tyr Ser Arg Ser Asp Thr Val Leu Gly Gly Phe Asp Cys
 115 120 125
 Met Gly Leu Leu Val Leu Cys Lys Ser Gly Pro Ile Cys Gln Arg Asp
 130 135 140
 Asn Gln Val Asp Pro Thr Ala Leu Cys His Cys Arg Val Asp Leu Ser
 145 150 155 160
 Ser Val Asp Cys Cys Lys Val Asn Lys Ile Ser Thr Asn Ser Ser Thr
 165 170 175
 Thr Ser Glu Pro Gln Lys Thr Asn Pro Ala Trp Pro Ser Gln Asp Asn
 180 185 190
 Thr Asp Ser Asp Pro Asn Pro Gln Gly Ile Thr Thr Ser Thr Ala Thr
 195 200 205
 Leu Leu Ser Thr Ser Leu Gly Leu Met Leu Thr Ser Lys Thr Gly Thr
 210 215 220
 His Lys Ser Gly Pro Pro Gln Ala Leu Pro Gly Ser Asn Thr Asn Gly
 225 230 235 240
 Lys Thr Thr Thr Asp Arg Glu Pro Gly Pro Thr Asn Gln Pro Asn Ser
 245 250 255
 Thr Thr Asn Gly Gln His Asn Lys His Thr Gln Arg Met Thr Pro Pro
 260 265 270
 Pro Ser His Asp Asn Thr Arg Thr Ile Leu Gln His Thr Thr Pro Trp
 275 280 285
 Glu Lys Thr Phe Ser Thr Tyr Lys Pro Thr His Ser Pro Thr Asn Glu
 290 295 300
 Ser Asp Gln Ser Leu Pro Thr Thr Gln Asn Ser Ile Asn Cys Glu His
 305 310 315 320
 Phe Asp Pro Gln Gly Lys Glu Lys Ile Cys Tyr Arg Val Gly Ser Tyr
 325 330 335

Asn	Ser	Asn	Ile	Thr	Lys	Gln	Cys	Arg	Ile	Asp	Val	Pro	Leu	Cys	Ser
340							345						350		
Thr	Tyr	Ser	Thr	Val	Cys	Met	Lys	Thr	Tyr	Tyr	Thr	Glu	Pro	Phe	Asn
355							360						365		
Cys	Trp	Arg	Arg	Ile	Trp	Arg	Cys	Leu	Cys	Asp	Asp	Gly	Val	Gly	Leu
370							375						380		
Val	Glu	Trp	Cys	Cys	Thr	Ser									
385							390								

<210> 17
<211> 414
<212> PRT
<213> rhinotracheitis virus

<400> 17																
Met	Gly	Ser	Glu	Leu	Tyr	Ile	Ile	Glu	Gly	Val	Ser	Ser	Ser	Glu	Ile	
1							5				10				15	
Val	Leu	Lys	Gln	Val	Leu	Arg	Arg	Ser	Gln	Lys	Ile	Leu	Leu	Gly	Leu	
20										25				30		
Val	Leu	Ser	Ala	Leu	Gly	Leu	Thr	Leu	Thr	Ser	Thr	Ile	Val	Ile	Ser	
35										40				45		
Ile	Cys	Ile	Ser	Val	Glu	Gln	Val	Lys	Leu	Arg	Gln	Cys	Val	Asp	Thr	
50										55				60		
Tyr	Trp	Ala	Glu	Asn	Gly	Ser	Leu	His	Pro	Gly	Gln	Ser	Thr	Glu	Asn	
65										70				75		80
Thr	Ser	Thr	Arg	Gly	Lys	Thr	Thr	Thr	Lys	Asp	Pro	Arg	Arg	Leu	Gln	
										85				90		95
Ala	Thr	Gly	Ala	Gly	Lys	Phe	Glu	Ser	Cys	Gly	Tyr	Val	Gln	Val	Val	
										100				105		110
Asp	Gly	Asp	Met	His	Asp	Arg	Ser	Tyr	Ala	Val	Leu	Gly	Gly	Val	Asp	
										115				120		125
Cys	Leu	Gly	Leu	Leu	Ala	Leu	Cys	Glu	Ser	Gly	Pro	Ile	Cys	Gln	Gly	
										130				135		140
Asp	Thr	Trp	Ser	Glu	Asp	Gly	Asn	Phe	Cys	Arg	Cys	Thr	Phe	Ser	Ser	
										145				150		155
His	Gly	Val	Ser	Cys	Cys	Lys	Pro	Lys	Ser	Lys	Ala	Thr	Thr	Ala		
										165				170		175
Gln	Arg	Asn	Ser	Lys	Pro	Ala	Asn	Ser	Lys	Ser	Thr	Pro	Pro	Val	His	
										180				185		190
Ser	Asp	Arg	Ala	Ser	Lys	Glu	His	Asn	Pro	Ser	Gln	Gly	Glu	Gln	Pro	
										195				200		205
Arg	Arg	Gly	Pro	Thr	Ser	Ser	Lys	Thr	Thr	Ile	Ala	Ser	Thr	Pro	Ser	
										210				215		220
Thr	Glu	Asp	Thr	Ala	Lys	Pro	Thr	Ile	Ser	Lys	Pro	Lys	Leu	Thr	Ile	
										225				230		235
Arg	Pro	Ser	Gln	Arg	Gly	Pro	Ser	Gly	Ser	Thr	Lys	Ala	Ala	Ser	Ser	
										245				250		255
Thr	Pro	Ser	His	Lys	Thr	Asn	Thr	Arg	Gly	Thr	Ser	Lys	Thr	Thr	Asp	
										260				265		270
Gln	Arg	Pro	Arg	Thr	Gly	Pro	Thr	Pro	Glu	Arg	Pro	Arg	Gln	Thr	His	
										275				280		285
Ser	Thr	Ala	Thr	Pro	Pro	Pro	Thr	Thr	Pro	Ile	His	Lys	Gly	Arg	Ala	
										290				295		300
Pro	Thr	Pro	Lys	Pro	Thr	Thr	Asp	Leu	Lys	Val	Asn	Pro	Arg	Glu	Gly	
										305				310		315
Ser	Thr	Ser	Pro	Thr	Ala	Ile	Gln	Lys	Asn	Pro	Thr	Thr	Gln	Ser	Asn	
										325				330		335
Leu	Val	Asp	Cys	Thr	Leu	Ser	Asp	Pro	Asp	Glu	Pro	Gln	Arg	Ile	Cys	
										340				345		350
Tyr	Gln	Val	Gly	Thr	Tyr	Asn	Pro	Ser	Gln	Ser	Gly	Thr	Cys	Asn	Ile	
										355				360		365

Glu	Val	Pro	Lys	Cys	Ser	Thr	Tyr	Gly	His	Ala	Cys	Met	Ala	Thr	Leu
370						375				380					
Tyr	Asp	Thr	Pro	Phe	Asn	Cys	Trp	Arg	Arg	Thr	Arg	Arg	Cys	Ile	Cys
385					390				395				400		
Asp	Ser	Gly	Gly	Glu	Leu	Ile	Glu	Trp	Cys	Cys	Thr	Ser	Gln		
					405				410						

<210> 18
<211> 539
<212> PRT
<213> human Metapneumo virus

<400> 18															
Met	Ser	Trp	Lys	Val	Val	Ile	Ile	Phe	Ser	Leu	Leu	Ile	Thr	Pro	Gln
1				5					10				15		
His	Gly	Leu	Lys	Glu	Ser	Tyr	Leu	Glu	Ser	Cys	Ser	Thr	Ile	Thr	
						20			25			30			
Glu	Gly	Tyr	Leu	Ser	Val	Leu	Arg	Thr	Gly	Trp	Tyr	Thr	Asn	Val	Phe
					35			40			45				
Thr	Leu	Glu	Val	Gly	Asp	Val	Glu	Asn	Leu	Thr	Cys	Ala	Asp	Gly	Pro
					50			55			60				
Ser	Leu	Ile	Lys	Thr	Glu	Leu	Asp	Leu	Thr	Lys	Ser	Ala	Leu	Arg	Glu
					65			70			75			80	
Leu	Arg	Thr	Val	Ser	Ala	Asp	Gln	Leu	Ala	Arg	Glu	Glu	Gln	Ile	Glu
					85					90			95		
Asn	Pro	Arg	Gln	Ser	Arg	Phe	Val	Leu	Gly	Ala	Ile	Ala	Leu	Gly	Val
					100			105			110				
Ala	Thr	Ala	Ala	Ala	Val	Thr	Ala	Gly	Val	Ala	Ile	Ala	Lys	Thr	Ile
					115			120			125				
Arg	Leu	Glu	Ser	Glu	Val	Thr	Ala	Ile	Lys	Asn	Ala	Leu	Lys	Lys	Thr
					130			135			140				
Asn	Glu	Ala	Val	Ser	Thr	Leu	Gly	Asn	Gly	Val	Arg	Val	Leu	Ala	Thr
					145			150			155			160	
Ala	Val	Arg	Glu	Leu	Lys	Asp	Phe	Val	Ser	Lys	Asn	Leu	Thr	Arg	Ala
					165				170			175			
Ile	Asn	Lys	Asn	Lys	Cys	Asp	Ile	Ala	Asp	Leu	Lys	Met	Ala	Val	Ser
					180			185			190				
Phe	Ser	Gln	Phe	Asn	Arg	Arg	Phe	Leu	Asn	Val	Val	Arg	Gln	Phe	Ser
					195			200			205				
Asp	Asn	Ala	Gly	Ile	Thr	Pro	Ala	Ile	Ser	Leu	Asp	Leu	Met	Thr	Asp
					210			215			220				
Ala	Glu	Leu	Ala	Arg	Ala	Val	Ser	Asn	Met	Pro	Thr	Ser	Ala	Gly	Gln
					225			230			235			240	
Ile	Lys	Leu	Met	Leu	Glu	Asn	Arg	Ala	Met	Val	Arg	Arg	Lys	Gly	Phe
					245				250			255			
Gly	Ile	Leu	Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln
					260			265			270				
Leu	Pro	Ile	Phe	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Ile	Val	Lys	Ala
					275			280			285				
Ala	Pro	Ser	Cys	Ser	Gly	Lys	Lys	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg
					290			295			300				
Glu	Asp	Gln	Gly	Trp	Tyr	Cys	Gln	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr
					305			310			315			320	
Pro	Asn	Glu	Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp
					325				330			335			
Thr	Ala	Ala	Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Lys	Glu	Cys	Asn	Ile
					340				345			350			
Asn	Ile	Ser	Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His
					355				360			365			
Pro	Ile	Ser	Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys
					370			375			380				

Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
 385 390 395 400
 Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
 405 410 415
 Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
 420 425 430
 Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
 435 440 445
 Val Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
 450 455 460
 Glu Ser Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
 465 470 475 480
 Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
 485 490 495
 Leu Ile Ala Val Leu Gly Ser Thr Met Ile Leu Val Ser Val Phe Ile
 500 505 510
 Ile Ile Lys Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
 515 520 525
 Gly Val Thr Asn Asn Gly Phe Ile Pro His Asn
 530 535

<210> 19
 <211> 539
 <212> PRT
 <213> human Metapneumo virus

<400> 19
 Met Ser Trp Lys Val Val Ile Ile Phe Ser Leu Leu Ile Thr Pro Gln
 1 5 10 15
 His Gly Leu Lys Glu Ser Tyr Leu Glu Ser Cys Ser Thr Ile Thr
 20 25 30
 Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
 35 40 45
 Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Ser Asp Gly Pro
 50 55 60
 Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
 65 70 75 80
 Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
 85 90 95
 Asn Pro Arg Gln Ser Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
 100 105 110
 Ala Thr Ala Ala Val Thr Ala Gly Val Ala Ile Ala Lys Thr Ile
 115 120 125
 Arg Leu Glu Ser Glu Val Thr Ala Ile Lys Asn Ala Leu Lys Thr Thr
 130 135 140
 Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
 145 150 155 160
 Ala Val Arg Glu Leu Lys Asp Phe Val Ser Lys Asn Leu Thr Arg Ala
 165 170 175
 Ile Asn Lys Asn Cys Asp Ile Asp Asp Leu Lys Met Ala Val Ser
 180 185 190
 Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
 195 200 205
 Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
 210 215 220
 Ala Glu Leu Ala Arg Ala Val Ser Asn Met Pro Thr Ser Ala Gly Gln
 225 230 235 240
 Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
 245 250 255
 Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Thr Val Gln
 260 265 270

Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala
 275 280 285
 Ala Pro Ser Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg
 290 295 300
 Glu Asp Gln Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr
 305 310 315 320
 Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
 325 330 335
 Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile
 340 345 350
 Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
 355 360 365
 Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
 370 375 380
 Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
 385 390 395 400
 Lys Gln Leu Asn Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
 405 410 415
 Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
 420 425 430
 Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Phe Asp Pro
 435 440 445
 Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
 450 455 460
 Glu Asn Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Arg Ile
 465 470 475 480
 Leu Ser Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
 485 490 495
 Leu Ile Ala Val Leu Gly Ser Ser Met Ile Leu Val Ser Ile Phe Ile
 500 505 510
 Ile Ile Lys Thr Lys Lys Pro Thr Gly Ala Pro Pro Glu Leu Ser
 515 520 525
 Gly Val Thr Asn Asn Gly Phe Ile Pro His Ser
 530 535

<210> 20
 <211> 539
 <212> PRT
 <213> human Metapneumo virus

<400> 20
 Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
 1 5 10 15
 His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
 20 25 30
 Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
 35 40 45
 Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
 50 55 60
 Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
 65 70 75 80
 Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
 85 90 95
 Asn Pro Arg Gln Ser Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
 100 105 110
 Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile
 115 120 125
 Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Ala Leu Lys Gln Thr
 130 135 140
 Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
 145 150 155 160

Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
 165 170 175
 Ile Asn Arg Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
 180 185 190
 Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
 195 200 205
 Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
 210 215 220
 Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
 225 230 235 240
 Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
 245 250 255
 Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
 260 265 270
 Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala
 275 280 285
 Ala Pro Ser Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg
 290 295 300
 Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr
 305 310 315 320
 Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
 325 330 335
 Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
 340 345 350
 Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
 355 360 365
 Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
 370 375 380
 Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Trp Val Gly Ile Ile
 385 390 395 400
 Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
 405 410 415
 Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
 420 425 430
 Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Phe Asp Pro
 435 440 445
 Ile Lys Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
 450 455 460
 Glu Ser Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Lys Ile
 465 470 475 480
 Leu Asn Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Val Ile
 485 490 495
 Leu Val Ala Val Leu Gly Leu Thr Met Ile Ser Val Ser Ile Ile Ile
 500 505 510
 Ile Ile Lys Lys Thr Arg Lys Pro Thr Gly Ala Pro Pro Glu Leu Asn
 515 520 525
 Gly Val Thr Asn Gly Gly Phe Ile Pro His Ser
 530 535

<210> 21
 <211> 539
 <212> PRT
 <213> human Metapneumo virus

<400> 21
 Met Ser Trp Lys Val Met Ile Ile Ile Ser Leu Leu Ile Thr Pro Gln
 1 5 10 15
 His Gly Leu Lys Glu Ser Tyr Leu Glu Glu Ser Cys Ser Thr Ile Thr
 20 25 30
 Glu Gly Tyr Leu Ser Val Leu Arg Thr Gly Trp Tyr Thr Asn Val Phe
 35 40 45

Thr Leu Glu Val Gly Asp Val Glu Asn Leu Thr Cys Thr Asp Gly Pro
 50 55 60
 Ser Leu Ile Lys Thr Glu Leu Asp Leu Thr Lys Ser Ala Leu Arg Glu
 65 70 75 80
 Leu Lys Thr Val Ser Ala Asp Gln Leu Ala Arg Glu Glu Gln Ile Glu
 85 90 95
 Asn Pro Arg Gln Ser Arg Phe Val Leu Gly Ala Ile Ala Leu Gly Val
 100 105 110
 Ala Thr Ala Ala Ala Val Thr Ala Gly Ile Ala Ile Ala Lys Thr Ile
 115 120 125
 Arg Leu Glu Ser Glu Val Asn Ala Ile Lys Gly Ala Leu Lys Thr Thr
 130 135 140
 Asn Glu Ala Val Ser Thr Leu Gly Asn Gly Val Arg Val Leu Ala Thr
 145 150 155 160
 Ala Val Arg Glu Leu Lys Glu Phe Val Ser Lys Asn Leu Thr Ser Ala
 165 170 175
 Ile Asn Lys Asn Lys Cys Asp Ile Ala Asp Leu Lys Met Ala Val Ser
 180 185 190
 Phe Ser Gln Phe Asn Arg Arg Phe Leu Asn Val Val Arg Gln Phe Ser
 195 200 205
 Asp Asn Ala Gly Ile Thr Pro Ala Ile Ser Leu Asp Leu Met Thr Asp
 210 215 220
 Ala Glu Leu Ala Arg Ala Val Ser Tyr Met Pro Thr Ser Ala Gly Gln
 225 230 235 240
 Ile Lys Leu Met Leu Glu Asn Arg Ala Met Val Arg Arg Lys Gly Phe
 245 250 255
 Gly Ile Leu Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln
 260 265 270
 Leu Pro Ile Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala
 275 280 285
 Ala Pro Ser Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg
 290 295 300
 Glu Asp Gln Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr
 305 310 315 320
 Pro Asn Glu Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp
 325 330 335
 Thr Ala Ala Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile
 340 345 350
 Asn Ile Ser Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His
 355 360 365
 Pro Ile Ser Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys
 370 375 380
 Tyr Lys Gly Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile
 385 390 395 400
 Lys Gln Leu Pro Lys Gly Cys Ser Tyr Ile Thr Asn Gln Asp Ala Asp
 405 410 415
 Thr Val Thr Ile Asp Asn Thr Val Tyr Gln Leu Ser Lys Val Glu Gly
 420 425 430
 Glu Gln His Val Ile Lys Gly Arg Pro Val Ser Ser Ser Phe Asp Pro
 435 440 445
 Ile Arg Phe Pro Glu Asp Gln Phe Asn Val Ala Leu Asp Gln Val Phe
 450 455 460
 Glu Ser Ile Glu Asn Ser Gln Ala Leu Val Asp Gln Ser Asn Lys Ile
 465 470 475 480
 Leu Asn Ser Ala Glu Lys Gly Asn Thr Gly Phe Ile Ile Val Ile Ile
 485 490 495
 Leu Ile Ala Val Leu Gly Leu Thr Met Ile Ser Val Ser Ile Ile Ile
 500 505 510
 Ile Ile Lys Lys Thr Arg Lys Pro Thr Gly Ala Pro Pro Glu Leu Asn
 515 520 525
 Gly Val Thr Asn Gly Gly Phe Ile Pro His Ser
 530 535

<210> 22
<211> 1620
<212> DNA
<213> human Metapneumo virus

<400> 22
atgtcttggaa aagtgggtat catttttca ttgtaataa cacctaaca cggctttaaa 60
gagagctact tagaagagtc atgttagact ataactgaag gatatctcg tttctgagg 120
acagggttgtt acaccaatgt ttttacactg gaggttaggcg atgtagagaa ctttacatgt 180
gccgatggac ccagcttaat aaaaacagaa ttagacctga cccaaagtgc actaagagag 240
ctcagaacag tttctgtga tcaactggca agagaggagc aaattgaaaaa tcccagacaa 300
tctagattcg ttcttaggac aatagcaactc ggtgttgcgaa ctgcagctgc agttacagca 360
ggtgttgcggaa ttgcacaaac catccggctt gaaagtgaag taacagcaat taagaatgcc 420
ctcaaaaaga ccaatgaagc agtatctaca ttggggatg gatgtcggt gtggcaact 480
gcagtgagag agctgaaaaga ttttgcgac aagaatctaa cacgtgcaat caacaaaaac 540
aagtgcgaca ttgtgtgaccc gaaaatggcc gttagcttca gtcaattcaa cagaagggttc 600
ctaaatgttg tgccggcaatt ttcagacaac gctggaaataa caccagcaat atctttggac 660
ttaatgacag atgtgaact agccagact gtttccaaca tgccaaacatc tgaggacaa 720
ataaaactga tttttggagaa cctgtcaatg gtaagaagaa aagggttcgg aatcctgata 780
ggaggttacg gaagctccgt aatttacatg gtgcactgc caatcttgg gttttagac 840
acgccttgcgt ggatgataaa agcagcccc tcttgcgtg gaaaaaaaggg aaactatgtc 900
tgcctcttaa gagaagacca aggatgtt gttcaatg cagggtcaac tttttactac 960
ccaaatgaaa aagactgtga aacaagagga gaccatgtct tttgcgacac agcagcagga 1020
atcaatgttg ctgagcagtc aaagggtgc aacataaaaca tatctactac taattaccca 1080
tgcaaaatgtt gcacagggaa acatcctatc agtatgggtt cactatctcc ttttgggct 1140
tttgttgcgtt gctacaaggg agtgcgtgt tccattggca gcaacagact agggatcatc 1200
aagcaactga acaaaggctg ctcttataata accaaccaaac acgcagacac agtgacaata 1260
gacaacactg tataccatg aagcaagtt gaaggcgaac agcatgtt aaaaaggaaagg 1320
ccagtgtcaa gcagcttgc cccagtcaag tttctgtgaa atcaattcaa ttttgcactt 1380
gaccaagttt tcgagagcat tgagaacagt caggccttgg tggatcaatc aaacagaatc 1440
ctaagcagtg cagagaaagg aaacactggc ttcatcattg taataattt aattgtgtgc 1500
cttggctcta ccatgatcct agtgagttt ttatcataa taaagaaaaac aaagaaaaacc 1560
acaggagcac ctccagagct gatgtgtgc acaaacaatg gttcataacc acataattag 1620

<210> 23
<211> 1620
<212> DNA
<213> human Metapneumo virus

<400> 23
atgtcttggaa aagtgggtat catttttca ttgctaataa cacctaaca cggctttaaa 60
gagagctacc tagaagaatc atgttagact ataactgagg gatatcttag tttctgagg 120
acagggttgtt ataccaacgt ttttacatta gaggtgggtg atgtagaaaa ctttacatgt 180
tctgtatggac ctgccttaat aaaaacagaa ttagatctga cccaaagtgc actaagagag 240
ctcaaaaacag tctctgtga ccaattggca agagaggaaac aaattgagaa tcccagacaa 300
tcttaggttg ttcttaggac aatagcaactc ggtgttgcgaa cagcagctgc agtcacagca 360
ggtgttgcggaa ttgcacaaac catccggctt gagagtgaag tcacagcaat taagaatgcc 420
ctcaaaaacga ccaatgaagc agtatctaca ttggggatg gatgtcggt gtggcaact 480
gcagtgagag agctaaaaga ctttgcgac aagaatttaa ctgcgtcaat caacaaaaac 540
aagtgcgaca ttgtgtgaccc aaaaatggct gttagcttca gtcaattcaa cagaagggtt 600
ctaaatgttg tgccggcaatt ttcagacaat gctggaaataa caccagcaat atctttggac 660
ttaatgacag atgtgaact agccaggccc gtttctaaca tgccgacatc tgaggacaa 720
ataaaattga tttttggagaa ccgtgcgtat gtgcgaagaa aagggttcgg aatcctgata 780
gggggtctacg ggagctccgt aatttacacg gtgcagctgc caatcttgg cttttagac 840
acgccttgcgt ggatgataaa agcagcccc tcttgcgtt aaaaaaaaggg aaactatgtc 900
tgcctcttaa gagaagacca agggtgtt gttcaatg cagggtcaac tttttactac 960
ccaaatgaga aagactgtga aacaagagga gaccatgtct tttgcgacac agcagcagga 1020
attaatgttg ctgagcaatc aaagggtgc aacatcaaca tatccactac aaattaccca 1080
tgcaaaatgtt gcacagggaa acatcctatc agtatgggtt cactgtctcc ttttgggct 1140
cttgggttgcgtt gctacaagg aatgtcggt tccattggca gcaacagact agggatcatc 1200

aaggcagctga acaaagggttgc tccttatata accaacccaag atgcagacac agtgacaata 1260
 gacaacactg tatatcagct aagcaaaagt gagggtaac agcatttat aaaaggcaga 1320
 ccagtgtcaa gcagcttgc tccaatcaag ttctctgaag atcaattcaa ttttcactt 1380
 gaccaagtt ttgagaacat tgaaaacagc caggccttag tagatcaatc aaacagaatc 1440
 ctaagcagtg cagagaaagg gaatactggc ttatcattg taataattct aattgctgtc 1500
 ctggctcta gcatgatcct agtgagcatt tcattataa tcaagaaaac aaagaaacca 1560
 acgggagcac ctccagagct gagtggtgtc acaaacaatg gttcataacc acacagttag 1620

<210> 24
<211> 1620
<212> DNA
<213> human Metapneumo virus

<400> 24
 atgtcttgc aagtgtatcatcattcg ttactcataa caccccagca cgggctaaag 60
 gagagttatt tggaagaatc atgtgtact ataaactgagg gatacctcag ttttttaaga 120
 acaggcgtgtt acactaatgt ctccacatta gaagttggtg atgttggaaa ttttacatgt 180
 actgtggac ctatgttaat caaaacagaa cttgatctaa caaaaagtgc tttaaggaa 240
 ctcaaaaacag tttctgtca tcagttggcg agagaggcgc aaattgaaaa tcccagacaa 300
 tcaagatttgc ttttaggtgc gatagcttc ggagttgcta cagcagcagc agtcacagca 360
 ggcattgcaaa tagccaaaac cataaggcgtt gagagtgggg tgaatgcaat taaaggtgt 420
 ctcaaaacaaa ctaatgaagc agtattccaca ttagggatg gtgtgcgggt cctagccact 480
 gcagtggagag agctaaaaga atttgtggc aaaaacctga ctatgtcaat caacaggaaac 540
 aaatgtgaca ttgtgtatct gaagatggcgt gtcagcttc gtcattca cagaagattt 600
 ctaatgttg tgcggcagtt ttcagacataa gcagggataa caccaccaat atcattggac 660
 ctgtgactg atgtgtatgtt ggccagacgt gtatcataca tgccaaacatc tgcaggcag 720
 ataaaactga tttttggagaa cccgcgaatc gtaaggagaa aaggatttgg aatcttgata 780
 ggggtctacg gaagctctgt gatttacatg gttcaattgc cgatcttgg tgcattatgt 840
 acaccttgcgtt ggatcatcaa ggcagctccc tttgtctcgt aaaaaaaaaacgg gaattatgt 900
 tgcctctaa gagaggatca agggtggat ttttttttttggatc caggatctac tttttactac 960
 ccaaatgaaa aagactgcga aacaaggatgtt gatcatgtt tttgtgacac agcagcagg 1020
 atcaatgttg ctgagcaatc aagagaatgc aacatcaaca tatctactac caactaccca 1080
 tgcaaaagtca gcacaggaag acaccctata agcatggttt cactatcacc ttcgggtgt 1140
 ttggtggctt gttataaaagg ggtttagtgc tggatggca gcaattgggt tggatcatc 1200
 aaacaattac ccaaaaggctg ctcatatata accaaccagg atgcagacac tggatggatc 1260
 gacaataccg tttatcaact aagcaaaagttaa gaaggtgaac agcatgttataa aaaaagggaga 1320
 ccagtttcaa gcagtttgc tccaatcaag ttctctgagg atcagttcaat ttttgcgtt 1380
 gatcaagtct tcgaaagcat tgagaacatc caggcactatc tggaccatc aaaaacaaaatt 1440
 ctaaacatgtc cagaaaaagg aaacactggt ttcatatcgt tagtaattttt gtttgcgtt 1500
 ctggctcta ccatgatttc agtgagcattc atcatcataa tcaagaaaac aaggaagccc 1560
 acaggagcac ctccagagct gaatgggtgc accaacggcg gtttcataacc acatagttag 1620

<210> 25
<211> 1620
<212> DNA
<213> human Metapneumo virus

<400> 25
 atgtcttgc aagtgtatcatcattcg ttactcataa cacctcagca cggactaaaa 60
 gaaaggttatt tagaagaatc atgtgtact ataaactgagg gatatctcag ttttttaaga 120
 acagggtgtt acaccaatgt ctccacatta gaagttggtg atgttggaaa ttttacatgt 180
 actgtggac ctatgttaat caaaacagaa cttgacctaa caaaaagtgc ttttggggaa 240
 ctcaaaaacag tttctgtca tcagttggcg agagaagaac aaattgaaaa tcccagacaa 300
 tcaaggtttgc ttttaggtgc aatagcttc ggagttgcca cagcagcagc agtcacagca 360
 ggcattgcaaa tagccaaaac cataagactt gagagtgggg tgaatgcaat caaagggtgt 420
 ctcaaaacaaa ccaacggcgtt agtattccaca ttttttttttggatc gatgtgcgtt cctagccact 480
 gcagtaagag agctggaaatc atttgtggc aaaaacctga ctatgtcaat caacagaac 540
 aaatgtgaca ttgtgtatct gaagatggcgt gtcagcttc gtcattca cagaagattt 600
 ctaatgttg tgcggcagtt ttcagacataa gcagggataa caccaccaat atcattggac 660
 ctaatgtgactg atgtgtatgtt ggccagacgt gtatcataca tgccaaacatc tgcaggcag 720

ataaaaactaa tgtagagaa ccgtgcaatg gtgaggagaa aaggatttg aatcttgcata 780
 ggggtctacg gaagctctgt gatttacatg gtccagctgc cgatcttgg tgcatacatg 840
 acaccccttt ggataatcaa ggcagctccc tcttgttcag aaaaagatgg aaattatgct 900
 tgcctcctaa gagaggatca agggtgtat tgcaaaaaatg caggatccac tgttactac 960
 ccaaatgaaa aagactgcga aacaagaggt gatcatgttt tttgtgacac agcagcagg 1020
 atcaatgtt ctgagcaatc aagagaatgc aacatcaaca tatctaccac caactaccca 1080
 tgc当地 gcaacaggaag acaccctatc agcatggtt cactatcacc tctcggtct 1140
 ttggtagctt gctacaaggg ggttagctgc tcgattggca gtaatcggt tgaaataatc 1200
 aaacaactac ctaaaggctg ctcatacata actaaccagg acgcagacac tctaacaatt 1260
 gacaacactg tgc当地 aagcaaagtt gagggtaac agcatgtat aaaaggaga 1320
 ccagttcaa gcagtttga tccaaatcagg tttctgagg atcagttca tggcgctt 1380
 gatcaagtt ttgaaagcat tgaaaacagt caagcaactg tggaccagtc aacaaaatt 1440
 ctgaacagtg cagaaaaagg aaacactggt ttcatattt taataattt gattgctgt 1500
 cttgggttaa ccatgattc agtggcatc atcatcataa tcaaaaaaac aaggaagccc 1560
 acagggcac ctccagagct gaatggtacc accaacggcg gtttataacc gcataatc 1620

<210> 26
<211> 236
<212> PRT
<213> human Metapneumo virus

<400> 26
Met Glu Val Lys Val Glu Asn Ile Arg Thr Ile Asp Met Leu Lys Ala
1 5 10 15
Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
20 25 30
Leu Val Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
35 40 45
Leu Ile Ile Asn Tyr Lys Met Gln Lys Asn Thr Ser Glu Ser Glu His
50 55 60
His Thr Ser Ser Pro Met Glu Ser Ser Arg Glu Thr Pro Thr Val
65 70 75 80
Pro Thr Asp Asn Ser Asp Thr Asn Ser Ser Pro Gln His Pro Thr Gln
85 90 95
Gln Ser Thr Glu Gly Ser Thr Leu Tyr Phe Ala Ala Ser Ala Ser Ser
100 105 110
Pro Glu Thr Glu Pro Thr Ser Thr Pro Asp Thr Thr Asn Arg Pro Pro
115 120 125
Phe Val Asp Thr His Thr Thr Pro Pro Ser Ala Ser Arg Thr Lys Thr
130 135 140
Ser Pro Ala Val His Thr Lys Asn Asn Pro Arg Thr Ser Ser Arg Thr
145 150 155 160
His Ser Pro Pro Arg Ala Thr Thr Arg Thr Ala Arg Arg Thr Thr Thr
165 170 175
Leu Arg Thr Ser Ser Thr Arg Lys Arg Pro Ser Thr Ala Ser Val Gln
180 185 190
Pro Asp Ile Ser Ala Thr Thr His Lys Asn Glu Glu Ala Ser Pro Ala
195 200 205
Ser Pro Gln Thr Ser Ala Ser Thr Thr Arg Ile Gln Arg Lys Ser Val
210 215 220
Glu Ala Asn Thr Ser Thr Thr Tyr Asn Gln Thr Ser
225 230 235

<210> 27
<211> 219
<212> PRT
<213> human Metapneumo virus

<400> 27
Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala

1	5	10	15												
Arg	Val	Lys	Asn	Arg	Val	Ala	Arg	Ser	Lys	Cys	Phe	Lys	Asn	Ala	Ser
20	25	30													
Leu	Ile	Leu	Ile	Gly	Ile	Thr	Thr	Leu	Ser	Ile	Ala	Leu	Asn	Ile	Tyr
35	40	45													
Leu	Ile	Ile	Asn	Tyr	Thr	Ile	Gln	Lys	Thr	Thr	Ser	Glu	Ser	Glu	His
50	55	60													
His	Thr	Ser	Ser	Pro	Pro	Thr	Glu	Pro	Asn	Lys	Glu	Ala	Ser	Thr	Ile
65	70	75	80												
Ser	Thr	Asp	Asn	Pro	Asp	Ile	Asn	Pro	Ser	Ser	Gln	His	Pro	Thr	Gln
85	90	95													
Gln	Ser	Thr	Glu	Asn	Pro	Thr	Leu	Asn	Pro	Ala	Ala	Ser	Ala	Ser	Pro
100	105	110													
Ser	Glu	Thr	Glu	Pro	Ala	Ser	Thr	Pro	Asp	Thr	Thr	Asn	Arg	Leu	Ser
115	120	125													
Ser	Val	Asp	Arg	Ser	Thr	Ala	Gln	Pro	Ser	Glu	Ser	Arg	Thr	Lys	Thr
130	135	140													
Lys	Pro	Thr	Val	His	Thr	Ile	Asn	Asn	Pro	Asn	Thr	Ala	Ser	Ser	Thr
145	150	155	160												
Gln	Ser	Pro	Pro	Arg	Thr	Thr	Thr	Lys	Ala	Ile	Arg	Arg	Ala	Thr	Thr
165	170	175													
Phe	Arg	Met	Ser	Ser	Thr	Gly	Lys	Arg	Pro	Thr	Thr	Thr	Leu	Val	Gln
180	185	190													
Ser	Asp	Ser	Ser	Thr	Thr	Thr	Gln	Asn	His	Glu	Glu	Thr	Gly	Ser	Ala
195	200	205													
Asn	Pro	Gln	Ala	Ser	Ala	Ser	Thr	Met	Gln	Asn					
210	215														

<210> 28
<211> 224
<212> PRT
<213> human Metapneumo virus

<400> 28															
Met	Glu	Val	Arg	Val	Glu	Asn	Ile	Arg	Ala	Ile	Asp	Met	Phe	Lys	Ala
1	5	10	15												
Lys	Ile	Lys	Asn	Arg	Ile	Arg	Ser	Ser	Arg	Cys	Tyr	Arg	Asn	Ala	Thr
20	25	30													
Leu	Ile	Leu	Ile	Gly	Leu	Thr	Ala	Leu	Ser	Met	Ala	Leu	Asn	Ile	Phe
35	40	45													
Leu	Ile	Ile	Asp	His	Ala	Thr	Leu	Arg	Asn	Met	Ile	Lys	Thr	Glu	Asn
50	55	60													
Cys	Ala	Asn	Met	Pro	Ser	Ala	Glu	Pro	Ser	Lys	Lys	Thr	Pro	Met	Thr
65	70	75	80												
Ser	Thr	Ala	Gly	Pro	Asn	Thr	Lys	Pro	Asn	Pro	Gln	Gln	Ala	Thr	Gln
85	90	95													
Trp	Thr	Thr	Glu	Asn	Ser	Thr	Ser	Pro	Val	Ala	Thr	Pro	Glu	Gly	His
100	105	110													
Pro	Tyr	Thr	Gly	Thr	Thr	Gln	Thr	Ser	Asp	Thr	Thr	Ala	Pro	Gln	Gln
115	120	125													
Thr	Thr	Asp	Lys	His	Thr	Ala	Pro	Leu	Lys	Ser	Thr	Asn	Glu	Gln	Ile
130	135	140													
Thr	Gln	Thr	Thr	Glu	Lys	Lys	Thr	Ile	Arg	Ala	Thr	Thr	Gln	Lys	
145	150	155	160												
Arg	Glu	Lys	Gly	Lys	Glu	Asn	Thr	Asn	Gln	Thr	Thr	Ser	Thr	Ala	Ala
165	170	175													
Thr	Gln	Thr	Thr	Asn	Thr	Asn	Gln	Ile	Arg	Asn	Ala	Ser	Glu	Thr	
180	185	190													
Ile	Thr	Thr	Ser	Asp	Arg	Pro	Arg	Thr	Asp	Thr	Thr	Gln	Ser	Ser	
195	200	205													
Glu	Gln	Thr	Thr	Arg	Ala	Thr	Asp	Pro	Ser	Ser	Pro	Pro	His	His	Ala

210

215

220

<210> 29
<211> 236
<212> PRT
<213> human Metapneumo virus

<400> 29

Met	Glu	Val	Arg	Val	Glu	Asn	Ile	Arg	Ala	Ile	Asp	Met	Phe	Lys	Ala	
1					5					10					15	
Lys	Met	Lys	Asn	Arg	Ile	Arg	Ser	Ser	Lys	Cys	Tyr	Arg	Asn	Ala	Thr	
					20					25					30	
Leu	Ile	Leu	Ile	Gly	Leu	Thr	Ala	Leu	Ser	Met	Ala	Leu	Asn	Ile	Phe	
					35					40					45	
Leu	Ile	Ile	Asp	Tyr	Ala	Met	Leu	Lys	Asn	Met	Thr	Lys	Val	Glu	His	
					50					55					60	
Cys	Val	Asn	Met	Pro	Pro	Val	Glu	Pro	Ser	Lys	Thr	Pro	Met	Thr		
					65					70					80	
Ser	Ala	Val	Asp	Leu	Asn	Thr	Lys	Pro	Asn	Pro	Gln	Gln	Ala	Thr	Gln	
					85					90					95	
Leu	Ala	Ala	Glu	Asp	Ser	Thr	Ser	Leu	Ala	Ala	Thr	Ser	Glu	Asp	His	
					100					105					110	
Leu	His	Thr	Gly	Thr	Thr	Pro	Thr	Pro	Asp	Ala	Thr	Val	Ser	Gln	Gln	
					115					120					125	
Thr	Thr	Asp	Glu	Tyr	Thr	Thr	Leu	Leu	Arg	Ser	Thr	Asn	Arg	Gln	Thr	
					130					135					140	
Thr	Gln	Thr	Thr	Thr	Glu	Lys	Lys	Pro	Thr	Gly	Ala	Thr	Thr	Lys	Lys	
					145					150					160	
Glu	Thr	Thr	Arg	Thr	Thr	Ser	Thr	Ala	Ala	Thr	Gln	Thr	Leu	Asn		
					165					170					175	
Thr	Thr	Asn	Gln	Thr	Ser	Tyr	Val	Arg	Glu	Ala	Thr	Thr	Ser	Ala		
					180					185					190	
Arg	Ser	Arg	Asn	Ser	Ala	Thr	Thr	Gln	Ser	Ser	Asp	Gln	Thr	Thr	Gln	
					195					200					205	
Ala	Ala	Asp	Pro	Ser	Ser	Gln	Pro	His	His	Thr	Gln	Lys	Ser	Thr	Thr	
					210					215					220	
Thr	Thr	Tyr	Asn	Thr	Asp	Thr	Ser	Ser	Pro	Ser	Ser					
					225					230					235	

<210> 30
<211> 708
<212> DNA
<213> human Metapneumo virus

<400> 30

gaggtgaaag	tggagaacat	tcgaacaata	gatatgctca	aagcaagagt	aaaaaatcggt	60	
gtggcacgca	gcaaatgctt	taaaaatgcc	tctttggtcc	tcataggaat	aactacattg	120	
agtattgc	ccc	tcaatatcta	tctgatcata	aactataaaa	tgcaaaaaaaaaa	cacatctgaa	180
tcagaacac	at	acaccagctc	atcacccatg	gaatccagca	gagaaactcc	aacggtcccc	240
acagacaact	c	cagacaccaa	ctcaagccca	cagcatccaa	ctcaacagtc	cacagaaggc	300
tccacact	c	actttgc	ctcagcaagc	tcaccagaga	cagaaccaac	atcaacaccca	360
gatacaacaa	acc	ccccggcc	cttcgtcgac	acacacacaa	caccaccaag	cgcaaggcaga	420
acaaagacaa	gt	ccggc	ccacacaaa	aacaacccaa	ggacaagctc	tagaacacat	480
tctccaccac	gg	caac	aggacgca	cgcagaacca	ccactctccg	cacaaggcagc	540
acaagaaaga	gac	gtcc	agcatca	caacctgaca	ttagcgcaac	aacccacaaa	600
aacgaagaag	ca	atc	gagcccacaa	acatctgcaa	gcacacaacag	aatacaaagg	660
aaaagcgtgg	agg	acac	atcaacaaca	tacaaccaaa	ctagttaa		708

<210> 31
<211> 660

<212> DNA

<213> human Metapneumo virus

<400> 31

atggaggtaa aagttagagaa cattcgagca atagacatgc tcaaagcaag agtaaaaat 60
 cgtgtggcac gtagcaaatg cttaaaaat gcttcttaa tcctcatagg aataactaca 120
 ctgagtatag ctctcaatat ctatctgatc ataaaactaca caatacaaaa aaccacatcc 180
 gaatcagaac accacaccag ctcaccaccc acagaaccca acaaggaagc ttcaacaatc 240
 tccacagaca acccagacat caatccaagc tcacagcatc caactcaaca gtccacagaa 300
 aaccccacac tcaacccccgc agcatcagcg agcccatcg aaacagaacc agcatcaaca 360
 ccagacacaa caaacccgcct gtccctcgta gacaggtcca cagcacaacc aagtgaaagc 420
 agaacaaaaga caaaaccgc acgtccacaca atcaacaacc caaacacacgc ttccagtaca 480
 caatccccac cacggacaac aacgaaggca atccgcagag ccaccactt ccgcatgagc 540
 agcacagggaa aaagaccaac cacaacatta gtccagtccg acagcagcac cacaacccaa 600
 aatcatgaag aaacaggttc agcgaaccca caggcgtctg caagcacaat gcaaaactag 660

<210> 32

<211> 675

<212> DNA

<213> human Metapneumo virus

<400> 32

atggaagtaa gagtggagaa cattcgagcg atagacatgt tcaaagcaaa gataaaaaac 60
 cgtataagaa gcagcaggcg ctatagaaat gctacactga tccttattgg actaacagcg 120
 ttaagcatgg cacttaatat ttccctgtatc atcgatcatg caacattaag aaacatgatc 180
 aaaacagaaaa actgtgttaa catgccgtcg gcagaaccaa gaaaaaagac cccaatgacc 240
 tccacagcg gccccaaacac caaacccaaat ccacagcaag caacacagtg gaccacagag 300
 aactcaacat ccccagtgc aaccccgag ggcacatccat acacagggac aactcaaaca 360
 tcagacacaa cagccccca gcaaaccaca gacaaacaca cagcaccgt aaaaatcaacc 420
 aatgaacaga tcaccccgac aaccacagag aaaaagacaa tcagagcaac aacccaaaaaa 480
 agggaaaaag gaaaagaaaa cacaaccaa accacaagca cagctgcaac cccaaacaacc 540
 aacaccacca accaaatcg aaatgcaagt gagacaatca caacatccga cagacccaga 600
 actgacacca caacccaaag cagcgaacag acaacccggg caacagaccc aagctcccca 660
 ccacaccatg catag 675

<210> 33

<211> 711

<212> DNA

<213> human Metapneumo virus

<400> 33

atggaagtaa gagtggagaa cattcgggca atagacatgt tcaaagcaaa aatgaaaaac 60
 cgtataagaa gtagcaagtg ctatagaaat gctacactga tccttattgg attaacagca 120
 ttaagtatgg cacttaatat ttttttaatc attgattatg caatgttaaa aaacatgacc 180
 aaagtggAAC actgtgttaa tatgccggcg gtagaaccaa gcaagaagac cccaatgacc 240
 tctgcgttag acttaaacac caaacccaaat ccacagcagg caacacagtg ggccgcagag 300
 gattcaacat ctctcgacg aacctcgag gaccatctac acacagggac aactccaaca 360
 ccagatgcaa cagtctctca gcaaaccaca gacgagtaca caacattgtc gagatcaacc 420
 aacagacaga ccacccaaac aaccacagag aaaaagccaa ccggagcaac aacccaaaaaa 480
 gaaaccacaa ctgcgactac aagcacaagct gcaacccaa cactcaacac taccaaccaa 540
 actagctatg tgagagaggc aaccacaca tccgcccagat ccagaacag tgccacaact 600
 caaaggcagcg accaaacaac ccaggcagca gaccaagct cccaaaccaca ccatacacag 660
 aaaagcacaacaa caacaacata caacacagac acatctctc caagtagtta a 711

<210> 34

<211> 2005

<212> PRT

<213> human Metapneumo virus

<400> 34

Met Asp Pro Leu Asn Glu Ser Thr Val Asn Val Tyr Leu Pro Asp Ser

1	5	10	15												
Tyr	Leu	Lys	Gly	Val	Ile	Ser	Phe	Ser	Glu	Thr	Asn	Ala	Ile	Gly	Ser
				20			25		30						
Cys	Leu	Leu	Lys	Arg	Pro	Tyr	Leu	Lys	Asn	Asp	Asn	Thr	Ala	Lys	Val
				35			40		45						
Ala	Ile	Glu	Asn	Pro	Val	Ile	Glu	His	Val	Arg	Leu	Lys	Asn	Ala	Val
				50			55		60						
Asn	Ser	Lys	Met	Lys	Ile	Ser	Asp	Tyr	Lys	Ile	Val	Glu	Pro	Val	Asn
				65			70		75						80
Met	Gln	His	Glu	Ile	Met	Lys	Asn	Val	His	Ser	Cys	Glu	Leu	Thr	Leu
				85			90		95						
Leu	Lys	Gln	Phe	Leu	Thr	Arg	Ser	Lys	Asn	Ile	Ser	Thr	Leu	Lys	Leu
				100			105		110						
Asn	Met	Ile	Cys	Asp	Trp	Leu	Gln	Leu	Lys	Ser	Thr	Ser	Asp	Asp	Thr
				115			120		125						
Ser	Ile	Leu	Ser	Phe	Ile	Asp	Val	Glu	Phe	Ile	Pro	Ser	Trp	Val	Ser
				130			135		140						
Asn	Trp	Phe	Ser	Asn	Trp	Tyr	Asn	Leu	Asn	Lys	Leu	Ile	Leu	Glu	Phe
				145			150		155						160
Arg	Lys	Glu	Glu	Val	Ile	Arg	Thr	Gly	Ser	Ile	Leu	Cys	Arg	Ser	Leu
				165			170		175						
Gly	Lys	Leu	Val	Phe	Val	Val	Ser	Ser	Tyr	Gly	Cys	Ile	Val	Lys	Ser
				180			185		190						
Asn	Lys	Ser	Lys	Arg	Val	Ser	Phe	Phe	Thr	Tyr	Asn	Gln	Leu	Leu	Thr
				195			200		205						
Trp	Lys	Asp	Val	Met	Leu	Ser	Arg	Phe	Asn	Ala	Asn	Phe	Cys	Ile	Trp
				210			215		220						
Val	Ser	Asn	Ser	Leu	Asn	Glu	Asn	Gln	Glu	Gly	Leu	Gly	Leu	Arg	Ser
				225			230		235						240
Asn	Leu	Gln	Gly	Ile	Leu	Thr	Asn	Lys	Leu	Tyr	Glu	Thr	Val	Asp	Tyr
				245			250		255						
Met	Leu	Ser	Leu	Cys	Cys	Asn	Glu	Gly	Phe	Ser	Leu	Val	Lys	Glu	Phe
				260			265		270						
Glu	Gly	Phe	Ile	Met	Ser	Glu	Ile	Leu	Arg	Ile	Thr	Glu	His	Ala	Gln
				275			280		285						
Phe	Ser	Thr	Arg	Phe	Arg	Asn	Thr	Leu	Leu	Asn	Gly	Leu	Thr	Asp	Gln
				290			295		300						
Leu	Thr	Lys	Leu	Lys	Asn	Lys	Arg	Leu	Arg	Val	His	Gly	Thr	Val	
				305			310		315						320
Leu	Glu	Asn	Asn	Asp	Tyr	Pro	Met	Tyr	Glu	Val	Val	Leu	Lys	Leu	Leu
				325			330		335						
Gly	Asp	Thr	Leu	Arg	Cys	Ile	Lys	Leu	Leu	Ile	Asn	Lys	Asn	Leu	Glu
				340			345		350						
Asn	Ala	Ala	Glu	Leu	Tyr	Tyr	Ile	Phe	Arg	Ile	Phe	Gly	His	Pro	Met
				355			360		365						
Val	Asp	Glu	Arg	Asp	Ala	Met	Asp	Ala	Val	Lys	Leu	Asn	Asn	Glu	Ile
				370			375		380						
Thr	Lys	Ile	Leu	Arg	Trp	Glu	Ser	Leu	Thr	Glu	Leu	Arg	Gly	Ala	Phe
				385			390		395						400
Ile	Leu	Arg	Ile	Ile	Lys	Gly	Phe	Val	Asp	Asn	Asn	Lys	Arg	Trp	Pro
				405			410		415						
Lys	Ile	Lys	Asn	Leu	Lys	Val	Leu	Ser	Lys	Arg	Trp	Thr	Met	Tyr	Phe
				420			425		430						
Lys	Ala	Lys	Ser	Tyr	Pro	Ser	Gln	Leu	Glu	Leu	Ser	Glu	Gln	Asp	Phe
				435			440		445						
Leu	Glu	Leu	Ala	Ala	Ile	Gln	Phe	Glu	Gln	Glu	Phe	Ser	Val	Pro	Glu
				450			455		460						
Lys	Thr	Asn	Leu	Glu	Met	Val	Leu	Asn	Asp	Lys	Ala	Ile	Ser	Pro	Pro
				465			470		475						480
Lys	Arg	Leu	Ile	Ile	Trp	Ser	Val	Tyr	Pro	Lys	Asn	Tyr	Leu	Pro	Glu
				485			490		495						
Ile	Lys	Asn	Arg	Tyr	Leu	Glu	Glu	Thr	Phe	Asn	Ala	Ser	Asp	Ser	Leu

500	505	510
Lys Thr Arg Arg Val Leu Glu Tyr	Tyr Leu Lys Asp Asn Lys	Phe Asp
515	520	525
Gln Lys Glu Leu Lys Ser Tyr Val Val Lys Gln Glu	Tyr Leu Asn Asp	
530	535	540
Lys Asp His Ile Val Ser Leu Thr Gly Lys Glu	Arg Glu Leu Ser Val	
545	550	555
Gly Arg Met Phe Ala Met Gln Pro Gly Lys Gln Arg	Gln Ile Gln Ile	560
565	570	575
Leu Ala Glu Lys Leu Leu Ala Asp Asn Ile Val Pro	Phe Pro Glu	
580	585	590
Thr Leu Thr Lys Tyr Gly Asp Leu Asp Leu Gln Arg	Ile Met Glu Ile	
595	600	605
Lys Ser Glu Leu Ser Ser Ile Lys Thr Arg Arg	Asn Asp Ser Tyr Asn	
610	615	620
Asn Tyr Ile Ala Arg Ala Ser Ile Val Thr Asp	Leu Ser Lys Phe Asn	
625	630	635
Gln Ala Phe Arg Tyr Glu Thr Thr Ala Ile Cys Ala	Asp Val Ala Asp	640
645	650	655
Glu Leu His Gly Thr Gln Ser Leu Phe Cys Trp	Leu His Leu Ile Val	
660	665	670
Pro Met Thr Thr Met Ile Cys Ala Tyr Arg His Ala	Pro Pro Glu Thr	
675	680	685
Lys Gly Glu Tyr Asp Ile Asp Lys Ile Glu Glu	Gln Ser Gly Leu Tyr	
690	695	700
Arg Tyr His Met Gly Gly Ile Glu Gly Trp	Cys Gln Lys Leu Trp Thr	
705	710	715
Met Glu Ala Ile Ser Leu Leu Asp Val Val Ser Val	Lys Thr Arg Cys	
725	730	735
Gln Met Thr Ser Leu Leu Asn Gly Asp Asn Gln Ser	Ile Asp Val Ser	
740	745	750
Lys Pro Val Lys Leu Ser Glu Gly Leu Asp Glu Val	Lys Ala Asp Tyr	
755	760	765
Ser Leu Ala Val Lys Met Leu Lys Glu Ile Arg Asp	Ala Tyr Arg Asn	
770	775	780
Ile Gly His Lys Leu Lys Glu Gly Glu Thr Tyr	Ile Ser Arg Asp Leu	
785	790	795
Gln Phe Ile Ser Lys Val Ile Gln Ser Glu Gly Val	Met His Pro Thr	
805	810	815
Pro Ile Lys Ile Leu Arg Val Gly Pro Trp Ile Asn	Thr Ile Leu	
820	825	830
Asp Asp Ile Lys Thr Ser Ala Glu Ser Ile Gly Ser	Leu Cys Gln Glu	
835	840	845
Leu Glu Phe Arg Gly Glu Ser Ile Ile Val Ser Leu	Ile Leu Arg Asn	
850	855	860
Phe Trp Leu Tyr Asn Leu Tyr Met His Glu Ser	Lys Gln His Pro Leu	
865	870	880
Ala Gly Lys Gln Leu Phe Lys Gln Leu Asn Lys	Thr Leu Thr Ser Val	
885	890	895
Gln Arg Phe Phe Glu Ile Lys Lys Glu Asn Glu Val	Val Asp Leu Trp	
900	905	910
Met Asn Ile Pro Met Gln Phe Gly Gly Asp Pro Val	Val Phe Tyr	
915	920	925
Arg Ser Phe Tyr Arg Arg Thr Pro Asp Phe Leu	Thr Glu Ala Ile Ser	
930	935	940
His Val Asp Ile Leu Leu Arg Ile Ser Ala Asn Ile	Arg Asn Glu Ala	
945	950	955
Lys Ile Ser Phe Phe Lys Ala Leu Leu Ser Ile	Glu Lys Asn Glu Arg	960
965	970	975
Ala Thr Leu Thr Thr Leu Met Arg Asp Pro Gln Ala	Val Gly Ser Glu	
980	985	990
Arg Gln Ala Lys Val Thr Ser Asp Ile Asn Arg Thr	Ala Val Thr Ser	

995	1000	1005
Ile Leu Ser Leu Ser Pro Asn Gln Leu Phe Ser Asp Ser Ala Ile His		
1010	1015	1020
Tyr Ser Arg Asn Glu Glu Glu Val Gly Ile Ile Ala Asp Asn Ile Thr		
1025	1030	1035
Pro Val Tyr Pro His Gly Leu Arg Val Leu Tyr Glu Ser Leu Pro Phe		
1045	1050	1055
His Lys Ala Glu Lys Val Val Asn Met Ile Ser Gly Thr Lys Ser Ile		
1060	1065	1070
Thr Asn Leu Leu Gln Arg Thr Ser Ala Ile Asn Gly Glu Asp Ile Asp		
1075	1080	1085
Arg Ala Val Ser Met Met Leu Glu Asn Leu Gly Leu Leu Ser Arg Ile		
1090	1095	1100
Leu Ser Val Val Val Asp Ser Ile Glu Ile Pro Thr Lys Ser Asn Gly		
1105	1110	1115
Arg Leu Ile Cys Cys Gln Ile Ser Arg Thr Leu Arg Glu Thr Ser Trp		
1125	1130	1135
Asn Asn Met Glu Ile Val Gly Val Thr Ser Pro Ser Ile Thr Thr Cys		
1140	1145	1150
Met Asp Val Ile Tyr Ala Thr Ser Ser His Leu Lys Gly Ile Ile Ile		
1155	1160	1165
Glu Lys Phe Ser Thr Asp Arg Thr Thr Arg Gly Gln Arg Gly Pro Lys		
1170	1175	1180
Ser Pro Trp Val Gly Ser Ser Thr Gln Glu Lys Lys Leu Val Pro Val		
1185	1190	1195
Tyr Asn Arg Gln Ile Leu Ser Lys Gln Gln Arg Glu Gln Leu Glu Ala		
1205	1210	1215
Ile Gly Lys Met Arg Trp Val Tyr Lys Gly Thr Pro Gly Leu Arg Arg		
1220	1225	1230
Leu Leu Asn Lys Ile Cys Leu Gly Ser Leu Gly Ile Ser Tyr Lys Cys		
1235	1240	1245
Val Lys Pro Leu Leu Pro Arg Phe Met Ser Val Asn Phe Leu His Arg		
1250	1255	1260
Leu Ser Val Ser Ser Arg Pro Met Glu Phe Pro Ala Ser Val Pro Ala		
1265	1270	1275
Tyr Arg Thr Thr Asn Tyr His Phe Asp Thr Ser Pro Ile Asn Gln Ala		
1285	1290	1295
Leu Ser Glu Arg Phe Gly Asn Glu Asp Ile Asn Leu Val Phe Gln Asn		
1300	1305	1310
Ala Ile Ser Cys Gly Ile Ser Ile Met Ser Val Val Glu Gln Leu Thr		
1315	1320	1325
Gly Arg Ser Pro Lys Gln Leu Val Leu Ile Pro Gln Leu Glu Glu Ile		
1330	1335	1340
Asp Ile Met Pro Pro Val Phe Gln Gly Lys Phe Asn Tyr Lys Leu		
1345	1350	1355
Val Asp Lys Ile Thr Ser Asp Gln His Ile Phe Ser Pro Asp Lys Ile		
1365	1370	1375
Asp Met Leu Thr Leu Gly Lys Met Leu Met Pro Thr Ile Lys Gly Gln		
1380	1385	1390
Lys Thr Asp Gln Phe Leu Asn Lys Arg Glu Asn Tyr Phe His Gly Asn		
1395	1400	1405
Asn Leu Ile Glu Ser Leu Ser Ala Ala Leu Ala Cys His Trp Cys Gly		
1410	1415	1420
Ile Leu Thr Glu Gln Cys Ile Glu Asn Asn Ile Phe Lys Lys Asp Trp		
1425	1430	1435
Gly Asp Gly Phe Ile Ser Asp His Ala Phe Met Asp Phe Lys Ile Phe		
1445	1450	1455
Leu Cys Val Phe Lys Thr Lys Leu Leu Cys Ser Trp Gly Ser Gln Gly		
1460	1465	1470
Lys Asn Ile Lys Asp Glu Asp Ile Val Asp Glu Ser Ile Asp Lys Leu		
1475	1480	1485
Leu Arg Ile Asp Asn Thr Phe Trp Arg Met Phe Ser Lys Val Met Phe		

1490	1495	1500
Glu Ser Lys Val Lys Lys Arg Ile Met Leu Tyr Asp Val Lys Phe Leu		
1505	1510	1515
Ser Leu Val Gly Tyr Ile Gly Phe Lys Asn Trp Phe Ile Glu Gln Leu		
1525	1530	1535
Arg Ser Ala Glu Leu His Glu Val Pro Trp Ile Val Asn Ala Glu Gly		
1540	1545	1550
Asp Leu Val Glu Ile Lys Ser Ile Lys Ile Tyr Leu Gln Leu Ile Glu		
1555	1560	1565
Gln Ser Leu Phe Leu Arg Ile Thr Val Leu Asn Tyr Thr Asp Met Ala		
1570	1575	1580
His Ala Leu Thr Arg Leu Ile Arg Lys Lys Leu Met Cys Asp Asn Ala		
1585	1590	1595
Leu Leu Thr Pro Ile Pro Ser Pro Met Val Asn Leu Thr Gln Val Ile		
1605	1610	1615
Asp Pro Thr Glu Gln Leu Ala Tyr Phe Pro Lys Ile Thr Phe Glu Arg		
1620	1625	1630
Leu Lys Asn Tyr Asp Thr Ser Ser Asn Tyr Ala Lys Gly Lys Leu Thr		
1635	1640	1645
Arg Asn Tyr Met Ile Leu Leu Pro Trp Gln His Val Asn Arg Tyr Asn		
1650	1655	1660
Phe Val Phe Ser Ser Thr Gly Cys Lys Val Ser Leu Lys Thr Cys Ile		
1665	1670	1675
Gly Lys Leu Met Lys Asp Leu Asn Pro Lys Val Leu Tyr Phe Ile Gly		
1685	1690	1695
Glu Gly Ala Gly Asn Trp Met Ala Arg Thr Ala Cys Glu Tyr Pro Asp		
1700	1705	1710
Ile Lys Phe Val Tyr Arg Ser Leu Lys Asp Asp Leu Asp His His Tyr		
1715	1720	1725
Pro Leu Glu Tyr Gln Arg Val Ile Gly Glu Leu Ser Arg Ile Ile Asp		
1730	1735	1740
Ser Gly Glu Gly Leu Ser Met Glu Thr Thr Asp Ala Thr Gln Lys Thr		
1745	1750	1755
His Trp Asp Leu Ile His Arg Val Ser Lys Asp Ala Leu Leu Ile Thr		
1765	1770	1775
Leu Cys Asp Ala Glu Phe Lys Asp Arg Asp Asp Phe Phe Lys Met Val		
1780	1785	1790
Ile Leu Trp Arg Lys His Val Leu Ser Cys Arg Ile Cys Thr Thr Tyr		
1795	1800	1805
Gly Thr Asp Leu Tyr Leu Phe Ala Lys Tyr His Ala Lys Asp Cys Asn		
1810	1815	1820
Val Lys Leu Pro Phe Phe Val Arg Ser Val Ala Thr Phe Ile Met Gln		
1825	1830	1835
Gly Ser Lys Leu Ser Gly Ser Glu Cys Tyr Ile Leu Leu Thr Leu Gly		
1845	1850	1855
His His Asn Asn Leu Pro Cys His Gly Glu Ile Gln Asn Ser Lys Met		
1860	1865	1870
Lys Ile Ala Val Cys Asn Asp Phe Tyr Ala Ala Lys Lys Leu Asp Asn		
1875	1880	1885
Lys Ser Ile Glu Ala Asn Cys Lys Ser Leu Leu Ser Gly Leu Arg Ile		
1890	1895	1900
Pro Ile Asn Lys Lys Glu Leu Asn Arg Gln Arg Arg Leu Leu Thr Leu		
1905	1910	1915
Gln Ser Asn His Ser Ser Val Ala Thr Val Gly Gly Ser Lys Val Ile		
1925	1930	1935
Glu Ser Lys Trp Leu Thr Asn Lys Ala Asn Thr Ile Ile Asp Trp Leu		
1940	1945	1950
Glu His Ile Leu Asn Ser Pro Lys Gly Glu Leu Asn Tyr Asp Phe Phe		
1955	1960	1965
Glu Ala Leu Glu Asn Thr Tyr Pro Asn Met Ile Lys Leu Ile Asp Asn		
1970	1975	1980
Leu Gly Asn Ala Glu Ile Lys Lys Leu Ile Lys Val Thr Gly Tyr Met		

1985	1990		
Leu Val Ser Lys Lys			
2005			

1995	2000
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<210> 35
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<212> PRT
<213> human Metapneumo virus

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Cys Leu Leu Lys Arg Pro Tyr Leu Lys Asn Asp Asn Thr Ala Lys Val
35 40 45
Ala Ile Glu Asn Pro Val Ile Glu His Val Arg Leu Lys Asn Ala Val
50 55 60
Asn Ser Lys Met Lys Ile Ser Asp Tyr Lys Val Val Glu Pro Val Asn
65 70 75 80
Met Gln His Glu Ile Met Lys Asn Val His Ser Cys Glu Leu Thr Leu
85 90 95
Leu Lys Gln Phe Leu Thr Arg Ser Lys Asn Ile Ser Thr Leu Lys Leu
100 105 110
Asn Met Ile Cys Asp Trp Leu Gln Leu Lys Ser Thr Ser Asp Asp Thr
115 120 125
Ser Ile Leu Ser Phe Ile Asp Val Glu Phe Ile Pro Ser Trp Val Ser
130 135 140
Asn Trp Phe Ser Asn Trp Tyr Asn Leu Asn Lys Leu Ile Leu Glu Phe
145 150 155 160
Arg Arg Glu Glu Val Ile Arg Thr Gly Ser Ile Leu Cys Arg Ser Leu
165 170 175
Gly Lys Leu Val Phe Ile Val Ser Ser Tyr Gly Cys Ile Val Lys Ser
180 185 190
Asn Lys Ser Lys Arg Val Ser Phe Phe Thr Tyr Asn Gln Leu Leu Thr
195 200 205
Trp Lys Asp Val Met Leu Ser Arg Phe Asn Ala Asn Phe Cys Ile Trp
210 215 220
Val Ser Asn Ser Leu Asn Glu Asn Gln Glu Gly Leu Gly Leu Arg Ser
225 230 235 240
Asn Leu Gln Gly Met Leu Thr Asn Lys Leu Tyr Glu Thr Val Asp Tyr
245 250 255
Met Leu Ser Leu Cys Cys Asn Glu Gly Phe Ser Leu Val Lys Glu Phe
260 265 270
Glu Gly Phe Ile Met Ser Glu Ile Leu Arg Ile Thr Glu His Ala Gln
275 280 285
Phe Ser Thr Arg Phe Arg Asn Thr Leu Leu Asn Gly Leu Thr Asp Gln
290 295 300
Leu Thr Lys Leu Lys Asn Lys Asn Arg Leu Arg Val His Gly Thr Val
305 310 315 320
Leu Glu Asn Asn Asp Tyr Pro Met Tyr Glu Val Val Leu Lys Leu Leu
325 330 335
Gly Asp Thr Leu Arg Cys Ile Lys Leu Leu Ile Asn Lys Asn Leu Glu
340 345 350
Asn Ala Ala Glu Leu Tyr Tyr Ile Phe Arg Ile Phe Gly His Pro Met
355 360 365
Val Asp Glu Arg Asp Ala Met Asp Ala Val Lys Leu Asn Asn Glu Ile
370 375 380
Thr Lys Ile Leu Arg Leu Glu Ser Leu Thr Glu Leu Arg Gly Ala Phe
385 390 395 400
Ile Leu Arg Ile Ile Lys Gly Phe Val Asp Asn Asn Lys Arg Trp Pro

405	410	415
Lys Ile Lys Asn Leu Ile Val Leu Ser	Lys Arg Trp Thr Met	Tyr Phe
420	425	430
Lys Ala Lys Asn Tyr Pro Ser Gln Leu Glu Leu Ser	Glu Gln Asp Phe	
435	440	445
Leu Glu Leu Ala Ala Ile Gln Phe Glu Gln Glu Phe	Ser Val Pro Glu	
450	455	460
Lys Thr Asn Leu Glu Met Val Leu Asn Asp	Lys Ala Ile Ser Pro Pro	
465	470	475
Lys Arg Leu Ile Trp Ser Val Tyr Pro Lys Asn Tyr	Leu Pro Glu Thr	
485	490	495
Ile Lys Asn Arg Tyr Leu Glu Glu Thr Phe Asn Ala Ser	Asp Ser Leu	
500	505	510
Lys Thr Arg Arg Val Leu Glu Tyr Tyr Leu Lys Asp	Asn Lys Phe Asp	
515	520	525
Gln Lys Glu Leu Lys Ser Tyr Val Val Arg Gln Glu	Tyr Leu Asn Asp	
530	535	540
Lys Glu His Ile Val Ser Leu Thr Gly Lys Glu Arg	Glu Leu Ser Val	
545	550	555
Gly Arg Met Phe Ala Met Gln Pro Gly Lys Gln Arg	Gln Ile Gln Ile	
565	570	575
Leu Ala Glu Lys Leu Ala Asp Asn Ile Val Pro Phe	Phe Pro Glu	
580	585	590
Thr Leu Thr Lys Tyr Gly Asp Leu Asp Leu Gln Arg	Ile Met Glu Ile	
595	600	605
Lys Ser Glu Leu Ser Ser Ile Lys Thr Arg Arg Asn	Asp Ser Tyr Asn	
610	615	620
Asn Tyr Ile Ala Arg Ala Ser Ile Val Thr Asp	Leu Ser Lys Phe Asn	
625	630	635
Gln Ala Phe Arg Tyr Glu Thr Thr Ala Ile Cys	Ala Asp Val Ala Asp	
645	650	655
Glu Leu His Gly Thr Gln Ser Leu Phe Cys Trp	Leu His Leu Ile Val	
660	665	670
Pro Met Thr Thr Met Ile Cys Ala Tyr Arg His Ala	Pro Pro Glu Thr	
675	680	685
Lys Gly Glu Tyr Asp Ile Asp Lys Ile Glu Glu	Gln Ser Gly Leu Tyr	
690	695	700
Arg Tyr His Met Gly Ile Glu Gly Trp Cys	Gln Lys Leu Trp Thr	
705	710	715
Met Glu Ala Ile Ser Leu Leu Asp Val Val Ser	Val Lys Thr Arg Cys	
725	730	735
Gln Met Thr Ser Leu Leu Asn Gly Asp Asn Gln Ser	Ile Asp Val Ser	
740	745	750
Lys Pro Val Lys Leu Ser Glu Gly Leu Asp Glu Val	Lys Ala Asp Tyr	
755	760	765
Arg Leu Ala Ile Lys Met Leu Lys Glu Ile Arg Asp	Ala Tyr Arg Asn	
770	775	780
Ile Gly His Lys Leu Lys Glu Gly Glu Thr	Tyr Ile Ser Arg Asp Leu	
785	790	795
Gln Phe Ile Ser Lys Val Ile Gln Ser Glu Gly Val	Met His Pro Thr	
805	810	815
Pro Ile Lys Lys Val Leu Arg Val Gly Pro Trp	Ile Asn Thr Ile Leu	
820	825	830
Asp Asp Ile Lys Thr Ser Ala Glu Ser Ile Gly Ser	Leu Cys Gln Glu	
835	840	845
Leu Glu Phe Arg Gly Glu Ser Ile Ile Val Ser	Leu Ile Leu Arg Asn	
850	855	860
Phe Trp Leu Tyr Asn Leu Tyr Met His Glu Ser	Lys Gln His Pro Leu	
865	870	875
Ala Gly Lys Gln Leu Phe Lys Gln Leu Asn Lys	Thr Leu Thr Ser Val	
885	890	895

Gln Arg Phe Phe Glu Ile Lys Lys Glu Asn Glu Val Val Asp Leu Trp
 900 905 910
 Met Asn Ile Pro Met Gln Phe Gly Gly Asp Pro Val Val Phe Tyr
 915 920 925
 Arg Ser Phe Tyr Arg Arg Thr Pro Asp Phe Leu Thr Glu Ala Ile Ser
 930 935 940
 His Val Asp Ile Leu Leu Lys Ile Ser Ala Asn Ile Lys Asn Glu Thr
 945 950 955 960
 Lys Val Ser Phe Phe Lys Ala Leu Leu Ser Ile Glu Lys Asn Glu Arg
 965 970 975
 Ala Thr Leu Thr Thr Leu Met Arg Asp Pro Gln Ala Val Gly Ser Glu
 980 985 990
 Arg Gln Ala Lys Val Thr Ser Asp Ile Asn Arg Thr Ala Val Thr Ser
 995 1000 1005
 Ile Leu Ser Leu Ser Pro Asn Gln Leu Phe Ser Asp Ser Ala Ile His
 1010 1015 1020
 Tyr Ser Arg Asn Glu Glu Val Gly Ile Ile Ala Glu Asn Ile Thr
 1025 1030 1035 1040
 Pro Val Tyr Pro His Gly Leu Arg Val Leu Tyr Glu Ser Leu Pro Phe
 1045 1050 1055
 His Lys Ala Glu Lys Val Val Asn Met Ile Ser Gly Thr Lys Ser Ile
 1060 1065 1070
 Thr Asn Leu Leu Gln Arg Thr Ser Ala Ile Asn Gly Glu Asp Ile Asp
 1075 1080 1085
 Arg Ala Val Ser Met Met Leu Glu Asn Leu Gly Leu Leu Ser Arg Ile
 1090 1095 1100
 Leu Ser Val Val Val Asp Ser Ile Glu Ile Pro Ile Lys Ser Asn Gly
 1105 1110 1115 1120
 Arg Leu Ile Cys Cys Gln Ile Ser Arg Thr Leu Arg Glu Thr Ser Trp
 1125 1130 1135
 Asn Asn Met Glu Ile Val Gly Val Thr Ser Pro Ser Ile Thr Thr Cys
 1140 1145 1150
 Met Asp Val Ile Tyr Ala Thr Ser Ser His Leu Lys Gly Ile Ile Ile
 1155 1160 1165
 Glu Lys Phe Ser Thr Asp Arg Thr Thr Arg Gly Gln Arg Gly Pro Lys
 1170 1175 1180
 Ser Pro Trp Val Gly Ser Ser Thr Gln Glu Lys Leu Val Pro Val
 1185 1190 1195 1200
 Tyr Asn Arg Gln Ile Leu Ser Lys Gln Gln Arg Glu Gln Leu Glu Ala
 1205 1210 1215
 Ile Gly Lys Met Arg Trp Val Tyr Lys Gly Thr Pro Gly Leu Arg Arg
 1220 1225 1230
 Leu Leu Asn Lys Ile Cys Leu Gly Ser Leu Gly Ile Ser Tyr Lys Cys
 1235 1240 1245
 Val Lys Pro Leu Leu Pro Arg Phe Met Ser Val Asn Phe Leu His Arg
 1250 1255 1260
 Leu Ser Val Ser Ser Arg Pro Met Glu Phe Pro Ala Ser Val Pro Ala
 1265 1270 1275 1280
 Tyr Arg Thr Thr Asn Tyr His Phe Asp Thr Ser Pro Ile Asn Gln Ala
 1285 1290 1295
 Leu Ser Glu Arg Phe Gly Asn Glu Asp Ile Asn Leu Val Phe Gln Asn
 1300 1305 1310
 Ala Ile Ser Cys Gly Ile Ser Ile Met Ser Val Val Glu Gln Leu Thr
 1315 1320 1325
 Gly Arg Ser Pro Lys Gln Leu Val Leu Ile Pro Gln Leu Glu Glu Ile
 1330 1335 1340
 Asp Ile Met Pro Pro Val Phe Gln Gly Lys Phe Asn Tyr Lys Leu
 1345 1350 1355 1360
 Val Asp Lys Ile Thr Ser Asp Gln His Ile Phe Ser Pro Asp Lys Ile
 1365 1370 1375
 Asp Met Leu Thr Leu Gly Lys Met Leu Met Pro Thr Ile Lys Gly Gln
 1380 1385 1390

Lys Thr Asp Gln Phe Leu Asn Lys Arg Glu Asn Tyr Phe His Gly Asn
 1395 1400 1405
 Asn Leu Ile Glu Ser Leu Ser Ala Ala Leu Ala Cys His Trp Cys Gly
 1410 1415 1420
 Ile Leu Thr Glu Gln Cys Ile Glu Asn Asn Ile Phe Lys Lys Asp Trp
 1425 1430 1435 1440
 Gly Asp Gly Phe Ile Ser Asp His Ala Phe Met Asp Phe Lys Ile Phe
 1445 1450 1455
 Leu Cys Val Phe Lys Thr Lys Leu Leu Cys Ser Trp Gly Ser Gln Gly
 1460 1465 1470
 Lys Asn Ile Lys Asp Glu Asp Ile Val Asp Glu Ser Ile Asp Lys Leu
 1475 1480 1485
 Leu Arg Ile Asp Asn Thr Phe Trp Arg Met Phe Ser Lys Val Met Phe
 1490 1495 1500
 Glu Pro Lys Val Lys Lys Arg Ile Met Leu Tyr Asp Val Lys Phe Leu
 1505 1510 1515 1520
 Ser Leu Val Gly Tyr Ile Gly Phe Lys Asn Trp Phe Ile Glu Gln Leu
 1525 1530 1535
 Arg Ser Ala Glu Leu His Glu Ile Pro Trp Ile Val Asn Ala Glu Gly
 1540 1545 1550
 Asp Leu Val Glu Ile Lys Ser Ile Lys Ile Tyr Leu Gln Leu Ile Glu
 1555 1560 1565
 Gln Ser Leu Phe Leu Arg Ile Thr Val Leu Asn Tyr Thr Asp Met Ala
 1570 1575 1580
 His Ala Leu Thr Arg Leu Ile Arg Lys Lys Leu Met Cys Asp Asn Ala
 1585 1590 1595 1600
 Leu Leu Thr Pro Ile Ser Ser Pro Met Val Asn Leu Thr Gln Val Ile
 1605 1610 1615
 Asp Pro Thr Thr Gln Leu Asp Tyr Phe Pro Lys Ile Thr Phe Glu Arg
 1620 1625 1630
 Leu Lys Asn Tyr Asp Thr Ser Ser Asn Tyr Ala Lys Gly Lys Leu Thr
 1635 1640 1645
 Arg Asn Tyr Met Ile Leu Leu Pro Trp Gln His Val Asn Arg Tyr Asn
 1650 1655 1660
 Phe Val Phe Ser Ser Thr Gly Cys Lys Val Ser Leu Lys Thr Cys Ile
 1665 1670 1675 1680
 Gly Lys Leu Met Lys Asp Leu Asn Pro Lys Val Leu Tyr Phe Ile Gly
 1685 1690 1695
 Glu Gly Ala Gly Asn Trp Met Ala Arg Thr Ala Cys Glu Tyr Pro Asp
 1700 1705 1710
 Ile Lys Phe Val Tyr Arg Ser Leu Lys Asp Asp Leu Asp His His Tyr
 1715 1720 1725
 Pro Leu Glu Tyr Gln Arg Val Ile Gly Glu Leu Ser Arg Ile Ile Asp
 1730 1735 1740
 Ser Gly Glu Gly Leu Ser Met Glu Thr Thr Asp Ala Thr Gln Lys Thr
 1745 1750 1755 1760
 His Trp Asp Leu Ile His Arg Val Ser Lys Asp Ala Leu Leu Ile Thr
 1765 1770 1775
 Leu Cys Asp Ala Glu Phe Lys Asp Arg Asp Asp Phe Phe Lys Met Val
 1780 1785 1790
 Ile Leu Trp Arg Lys His Val Leu Ser Cys Arg Ile Cys Thr Thr Tyr
 1795 1800 1805
 Gly Thr Asp Leu Tyr Leu Phe Ala Lys Tyr His Ala Lys Asp Cys Asn
 1810 1815 1820
 Val Lys Leu Pro Phe Phe Val Arg Ser Val Ala Thr Phe Ile Met Gln
 1825 1830 1835 1840
 Gly Ser Lys Leu Ser Gly Ser Glu Cys Tyr Ile Leu Leu Thr Leu Gly
 1845 1850 1855
 His His Asn Ser Leu Pro Cys His Gly Glu Ile Gln Asn Ser Lys Met
 1860 1865 1870
 Lys Ile Ala Val Cys Asn Asp Phe Tyr Ala Ala Lys Lys Leu Asp Asn
 1875 1880 1885

Lys Ser Ile Glu Ala Asn Cys Lys Ser Leu Leu Ser Gly Leu Arg Ile
 1890 1895 1900
 Pro Ile Asn Lys Lys Glu Leu Asp Arg Gln Arg Arg Leu Leu Thr Leu
 1905 1910 1915 1920
 Gln Ser Asn His Ser Ser Val Ala Thr Val Gly Gly Ser Lys Ile Ile
 1925 1930 1935
 Glu Ser Lys Trp Leu Thr Asn Lys Ala Ser Thr Ile Ile Asp Trp Leu
 1940 1945 1950
 Glu His Ile Leu Asn Ser Pro Lys Gly Glu Leu Asn Tyr Asp Phe Phe
 1955 1960 1965
 Glu Ala Leu Glu Asn Thr Tyr Pro Asn Met Ile Lys Leu Ile Asp Asn
 1970 1975 1980
 Leu Gly Asn Ala Glu Ile Lys Lys Leu Ile Lys Val Thr Gly Tyr Met
 1985 1990 1995 2000
 Leu Val Ser Lys Lys
 2005

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 Cys Leu Leu Lys Arg Pro Tyr Leu Lys Asn Asp Asn Thr Ala Lys Val
 35 40 45
 Ala Val Glu Asn Pro Val Val Glu His Val Arg Leu Arg Asn Ala Val
 50 55 60
 Met Thr Lys Met Lys Ile Ser Asp Tyr Lys Val Val Glu Pro Val Asn
 65 70 75 80
 Met Gln His Glu Ile Met Lys Asn Ile His Ser Cys Glu Leu Thr Leu
 85 90 95
 Leu Lys Gln Phe Leu Thr Arg Ser Lys Asn Ile Ser Ser Leu Lys Leu
 100 105 110
 Asn Met Ile Cys Asp Trp Leu Gln Leu Lys Ser Thr Ser Asp Asn Thr
 115 120 125
 Ser Ile Leu Asn Phe Ile Asp Val Glu Phe Ile Pro Val Trp Val Ser
 130 135 140
 Asn Trp Phe Ser Asn Trp Tyr Asn Leu Asn Lys Leu Ile Leu Glu Phe
 145 150 155 160
 Arg Arg Glu Glu Val Ile Arg Thr Gly Ser Ile Leu Cys Arg Ser Leu
 165 170 175
 Gly Lys Leu Val Phe Ile Val Ser Ser Tyr Gly Cys Val Val Lys Ser
 180 185 190
 Asn Lys Ser Lys Arg Val Ser Phe Phe Thr Tyr Asn Gln Leu Leu Thr
 195 200 205
 Trp Lys Asp Val Met Leu Ser Arg Phe Asn Ala Asn Phe Cys Ile Trp
 210 215 220
 Val Ser Asn Asn Leu Asn Lys Asn Gln Glu Gly Leu Gly Leu Arg Ser
 225 230 235 240
 Asn Leu Gln Gly Met Leu Thr Asn Lys Leu Tyr Glu Thr Val Asp Tyr
 245 250 255
 Met Leu Ser Leu Cys Cys Asn Glu Gly Phe Ser Leu Val Lys Glu Phe
 260 265 270
 Glu Gly Phe Ile Met Ser Glu Ile Leu Lys Ile Thr Glu His Ala Gln
 275 280 285
 Phe Ser Thr Arg Phe Arg Asn Thr Leu Leu Asn Gly Leu Thr Glu Gln
 290 295 300

Leu Ser Val Leu Lys Ala Lys Asn Arg Ser Arg Val Leu Gly Thr Ile
 305 310 315 320
 Leu Glu Asn Asn Asn Tyr Pro Met Tyr Glu Val Val Leu Lys Leu Leu
 325 330 335
 Gly Asp Thr Leu Lys Ser Ile Lys Leu Leu Ile Asn Lys Asn Leu Glu
 340 345 350
 Asn Ala Ala Glu Leu Tyr Tyr Ile Phe Arg Ile Phe Gly His Pro Met
 355 360 365
 Val Asp Glu Arg Glu Ala Met Asp Ala Val Lys Leu Asn Asn Glu Ile
 370 375 380
 Thr Lys Ile Leu Lys Leu Glu Ser Leu Thr Glu Leu Arg Gly Ala Phe
 385 390 395 400
 Ile Leu Arg Ile Ile Lys Gly Phe Val Asp Asn Asn Lys Arg Trp Pro
 405 410 415
 Lys Ile Lys Asn Leu Lys Val Leu Ser Lys Arg Trp Ala Met Tyr Phe
 420 425 430
 Lys Ala Lys Ser Tyr Pro Ser Gln Leu Glu Leu Ser Val Gln Asp Phe
 435 440 445
 Leu Glu Leu Ala Ala Val Gln Phe Glu Gln Glu Phe Ser Val Pro Glu
 450 455 460
 Lys Thr Asn Leu Glu Met Val Leu Asn Asp Lys Ala Ile Ser Pro Pro
 465 470 475 480
 Lys Lys Leu Ile Trp Ser Val Tyr Pro Lys Asn Tyr Leu Pro Glu Thr
 485 490 495
 Ile Lys Asn Gln Tyr Leu Glu Glu Ala Phe Asn Ala Ser Asp Ser Gln
 500 505 510
 Arg Thr Arg Arg Val Leu Glu Phe Tyr Leu Lys Asp Cys Lys Phe Asp
 515 520 525
 Gln Lys Glu Leu Lys Arg Tyr Val Ile Lys Gln Glu Tyr Leu Asn Asp
 530 535 540
 Lys Asp His Ile Val Ser Leu Thr Gly Lys Glu Arg Glu Leu Ser Val
 545 550 555 560
 Gly Arg Met Phe Ala Met Gln Pro Gly Lys Gln Arg Gln Ile Gln Ile
 565 570 575
 Leu Ala Glu Lys Leu Leu Ala Asp Asn Ile Val Pro Phe Phe Pro Glu
 580 585 590
 Thr Leu Thr Lys Tyr Gly Asp Leu Asp Leu Gln Arg Ile Met Glu Ile
 595 600 605
 Lys Ser Glu Leu Ser Ser Ile Lys Thr Arg Lys Asn Asp Ser Tyr Asn
 610 615 620
 Asn Tyr Ile Ala Arg Ala Ser Ile Val Thr Asp Leu Ser Lys Phe Asn
 625 630 635 640
 Gln Ala Phe Arg Tyr Glu Thr Thr Ala Ile Cys Ala Asp Val Ala Asp
 645 650 655
 Glu Leu His Gly Thr Gln Ser Leu Phe Cys Trp Leu His Leu Ile Val
 660 665 670
 Pro Met Thr Thr Met Ile Cys Ala Tyr Arg His Ala Pro Pro Glu Thr
 675 680 685
 Lys Gly Glu Tyr Asp Ile Asp Lys Ile Gln Glu Gln Ser Gly Leu Tyr
 690 695 700
 Arg Tyr His Met Gly Gly Ile Glu Gly Trp Cys Gln Lys Leu Trp Thr
 705 710 715 720
 Met Glu Ala Ile Ser Leu Leu Asp Val Val Ser Val Lys Thr Arg Cys
 725 730 735
 Gln Met Thr Ser Leu Leu Asn Gly Asp Asn Gln Ser Ile Asp Val Ser
 740 745 750
 Lys Pro Val Lys Leu Ser Glu Gly Ile Asp Glu Val Lys Ala Asp Tyr
 755 760 765
 Ser Leu Ala Ile Arg Met Leu Lys Glu Ile Arg Asp Ala Tyr Lys Asn
 770 775 780
 Ile Gly His Lys Leu Lys Glu Gly Glu Thr Tyr Ile Ser Arg Asp Leu
 785 790 795 800

Gln Phe Ile Ser Lys Val Ile Gln Ser Glu Gly Val Met His Pro Thr
 805 810 815
 Pro Ile Lys Lys Ile Leu Arg Val Gly Pro Trp Ile Asn Thr Ile Leu
 820 825 830
 Asp Asp Ile Lys Thr Ser Ala Glu Ser Ile Gly Ser Leu Cys Gln Glu
 835 840 845
 Leu Glu Phe Arg Gly Glu Ser Ile Leu Val Ser Leu Ile Leu Arg Asn
 850 855 860
 Phe Trp Leu Tyr Asn Leu Tyr Met Tyr Glu Ser Lys Gln His Pro Leu
 865 870 875 880
 Ala Gly Lys Gln Leu Phe Lys Gln Leu Asn Lys Thr Leu Thr Ser Val
 885 890 895
 Gln Arg Phe Phe Glu Leu Lys Lys Glu Asn Asp Val Val Asp Leu Trp
 900 905 910
 Met Asn Ile Pro Met Gln Phe Gly Gly Asp Pro Val Val Phe Tyr
 915 920 925
 Arg Ser Phe Tyr Arg Arg Thr Pro Asp Phe Leu Thr Glu Ala Ile Ser
 930 935 940
 His Val Asp Leu Leu Leu Lys Val Ser Asn Asn Ile Lys Asp Glu Thr
 945 950 955 960
 Lys Ile Arg Phe Phe Lys Ala Leu Leu Ser Ile Glu Lys Asn Glu Arg
 965 970 975
 Ala Thr Leu Thr Leu Met Arg Asp Pro Gln Ala Val Gly Ser Glu
 980 985 990
 Arg Gln Ala Lys Val Thr Ser Asp Ile Asn Arg Thr Ala Val Thr Ser
 995 1000 1005
 Ile Leu Ser Leu Ser Pro Asn Gln Leu Phe Cys Asp Ser Ala Ile His
 1010 1015 1020
 Tyr Ser Arg Asn Glu Glu Val Gly Ile Ile Ala Asp Asn Ile Thr
 1025 1030 1035 1040
 Pro Val Tyr Pro His Gly Leu Arg Val Leu Tyr Glu Ser Leu Pro Phe
 1045 1050 1055
 His Lys Ala Glu Lys Val Val Asn Met Ile Ser Gly Thr Lys Ser Ile
 1060 1065 1070
 Thr Asn Leu Leu Gln Arg Thr Ser Ala Ile Asn Gly Glu Asp Ile Asp
 1075 1080 1085
 Arg Ala Val Ser Met Met Leu Glu Asn Leu Gly Leu Leu Ser Arg Ile
 1090 1095 1100
 Leu Ser Val Ile Ile Asn Ser Ile Glu Ile Pro Ile Lys Ser Asn Gly
 1105 1110 1115 1120
 Arg Leu Ile Cys Cys Gln Ile Ser Lys Thr Leu Arg Glu Lys Ser Trp
 1125 1130 1135
 Asn Asn Met Glu Ile Val Gly Val Thr Ser Pro Ser Ile Val Thr Cys
 1140 1145 1150
 Met Asp Val Val Tyr Ala Thr Ser Ser His Leu Lys Gly Ile Ile Ile
 1155 1160 1165
 Glu Lys Phe Ser Thr Asp Lys Thr Thr Arg Gly Gln Arg Gly Pro Lys
 1170 1175 1180
 Ser Pro Trp Val Gly Ser Ser Thr Gln Glu Lys Leu Val Pro Val
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 Tyr Asn Arg Gln Ile Leu Ser Lys Gln Gln Lys Glu Gln Leu Glu Ala
 1205 1210 1215
 Ile Gly Lys Met Arg Trp Val Tyr Lys Gly Thr Pro Gly Leu Arg Arg
 1220 1225 1230
 Leu Leu Asn Lys Ile Cys Ile Gly Ser Leu Gly Ile Ser Tyr Lys Cys
 1235 1240 1245
 Val Lys Pro Leu Leu Pro Arg Phe Met Ser Val Asn Phe Leu His Arg
 1250 1255 1260
 Leu Ser Val Ser Ser Arg Pro Met Glu Phe Pro Ala Ser Val Pro Ala
 1265 1270 1275 1280
 Tyr Arg Thr Thr Asn Tyr His Phe Asp Thr Ser Pro Ile Asn Gln Ala
 1285 1290 1295

Leu Ser Glu Arg Phe Gly Asn Glu Asp Ile Asn Leu Val Phe Gln Asn
 1300 1305 1310
 Ala Ile Ser Cys Gly Ile Ser Ile Met Ser Val Val Glu Gln Leu Thr
 1315 1320 1325
 Gly Arg Ser Pro Lys Gln Leu Val Leu Ile Pro Gln Leu Glu Glu Ile
 1330 1335 1340
 Asp Ile Met Pro Pro Val Phe Gln Gly Lys Phe Asn Tyr Lys Leu
 1345 1350 1355 1360
 Val Asp Lys Ile Thr Ser Asp Gln His Ile Phe Ser Pro Asp Lys Ile
 1365 1370 1375
 Asp Ile Leu Thr Leu Gly Lys Met Leu Met Pro Thr Ile Lys Gly Gln
 1380 1385 1390
 Lys Thr Asp Gln Phe Leu Asn Lys Arg Glu Asn Tyr Phe His Gly Asn
 1395 1400 1405
 Asn Leu Ile Glu Ser Leu Ser Ala Ala Leu Ala Cys His Trp Cys Gly
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 1460 1465 1470
 Lys Asn Val Lys Asp Glu Asp Ile Ile Asp Glu Ser Ile Asp Lys Leu
 1475 1480 1485
 Leu Arg Ile Asp Asn Thr Phe Trp Arg Met Phe Ser Lys Val Met Phe
 1490 1495 1500
 Glu Ser Lys Val Lys Lys Arg Ile Met Leu Tyr Asp Val Lys Phe Leu
 1505 1510 1515 1520
 Ser Leu Val Gly Tyr Ile Gly Phe Lys Asn Trp Phe Ile Glu Gln Leu
 1525 1530 1535
 Arg Val Val Glu Leu His Glu Val Pro Trp Ile Val Asn Ala Glu Gly
 1540 1545 1550
 Glu Leu Val Glu Ile Lys Ser Ile Lys Ile Tyr Leu Gln Leu Ile Glu
 1555 1560 1565
 Gln Ser Leu Ser Leu Arg Ile Thr Val Leu Asn Tyr Thr Asp Met Ala
 1570 1575 1580
 His Ala Leu Thr Arg Leu Ile Arg Lys Lys Leu Met Cys Asp Asn Ala
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 Asp Pro Thr Thr Gln Leu Asp Tyr Phe Pro Arg Ile Ile Phe Glu Arg
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 1635 1640 1645
 Arg Asn Tyr Met Thr Leu Leu Pro Trp Gln His Val Asn Arg Tyr Asn
 1650 1655 1660
 Phe Val Phe Ser Ser Thr Gly Cys Lys Val Ser Leu Lys Thr Cys Ile
 1665 1670 1675 1680
 Gly Lys Leu Ile Lys Asp Leu Asn Pro Lys Val Leu Tyr Phe Ile Gly
 1685 1690 1695
 Glu Gly Ala Gly Asn Trp Met Ala Arg Thr Ala Cys Glu Tyr Pro Asp
 1700 1705 1710
 Ile Lys Phe Val Tyr Arg Ser Leu Lys Asp Asp Leu Asp His His Tyr
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 Pro Leu Glu Tyr Gln Arg Val Ile Gly Asp Leu Asn Arg Val Ile Asp
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 Ser Gly Glu Gly Leu Ser Met Glu Thr Thr Asp Ala Thr Gln Lys Thr
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 His Trp Asp Leu Ile His Arg Ile Ser Lys Asp Ala Leu Leu Ile Thr
 1765 1770 1775
 Leu Cys Asp Ala Glu Phe Lys Asn Arg Asp Asp Phe Phe Lys Met Val
 1780 1785 1790

Ile Leu Trp Arg Lys His Val Leu Ser Cys Arg Ile Cys Thr Ala Tyr
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 Gly Thr Asp Leu Tyr Leu Phe Ala Lys Tyr His Ala Val Asp Cys Asn
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 1845 1850 1855
 His His Asn Asn Leu Pro Cys His Gly Glu Ile Gln Asn Ser Lys Met
 1860 1865 1870
 Arg Ile Ala Val Cys Asn Asp Phe Tyr Ala Ser Lys Lys Leu Asp Asn
 1875 1880 1885
 Lys Ser Ile Glu Ala Asn Cys Lys Ser Leu Leu Ser Gly Leu Arg Ile
 1890 1895 1900
 Pro Ile Asn Lys Lys Glu Leu Asn Arg Gln Lys Lys Leu Leu Thr Leu
 1905 1910 1915 1920
 Gln Ser Asn His Ser Ser Ile Ala Thr Val Gly Gly Ser Lys Ile Ile
 1925 1930 1935
 Glu Ser Lys Trp Leu Lys Asn Lys Ala Ser Thr Ile Ile Asp Trp Leu
 1940 1945 1950
 Glu His Ile Leu Asn Ser Pro Lys Gly Glu Leu Asn Tyr Asp Phe Phe
 1955 1960 1965
 Glu Ala Leu Glu Asn Thr Tyr Pro Asn Met Ile Lys Leu Ile Asp Asn
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 35 40 45
 Ala Val Glu Asn Pro Val Val Glu His Val Arg Leu Arg Asn Ala Val
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 Met Thr Lys Met Lys Ile Ser Asp Tyr Lys Val Val Glu Pro Ile Asn
 65 70 75 80
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 Leu Lys Gln Phe Leu Thr Arg Ser Lys Asn Ile Ser Ser Leu Lys Leu
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 Ser Met Ile Cys Asp Trp Leu Gln Leu Lys Ser Thr Ser Asp Asn Thr
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 Ser Ile Leu Asn Phe Ile Asp Val Glu Phe Ile Pro Val Trp Val Ser
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 Asn Trp Phe Ser Asn Trp Tyr Asn Leu Asn Lys Leu Ile Leu Glu Phe
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 Arg Arg Glu Glu Val Ile Arg Thr Gly Ser Ile Leu Cys Arg Ser Leu
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 Gly Lys Leu Val Phe Ile Val Ser Ser Tyr Gly Cys Val Val Lys Ser
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 Asn Lys Ser Lys Arg Val Ser Phe Phe Thr Tyr Asn Gln Leu Leu Thr
 195 200 205

Trp Lys Asp Val Met Leu Ser Arg Phe Asn Ala Asn Phe Cys Ile Trp
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 Val Ser Asn Asn Leu Asn Lys Asn Gln Glu Gly Leu Gly Phe Arg Ser
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 245 250 255
 Met Leu Ser Leu Cys Ser Asn Glu Gly Phe Ser Leu Val Lys Glu Phe
 260 265 270
 Glu Gly Phe Ile Met Ser Glu Ile Leu Lys Ile Thr Glu His Ala Gln
 275 280 285
 Phe Ser Thr Arg Phe Arg Asn Thr Leu Leu Asn Gly Leu Thr Glu Gln
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 Leu Ser Met Leu Lys Ala Lys Asn Arg Ser Arg Val Leu Gly Thr Ile
 305 310 315 320
 Leu Glu Asn Asn Asp Tyr Pro Met Tyr Glu Val Val Leu Lys Leu Leu
 325 330 335
 Gly Asp Thr Leu Lys Ser Ile Lys Leu Leu Ile Asn Lys Asn Leu Glu
 340 345 350
 Asn Ala Ala Glu Leu Tyr Tyr Ile Phe Arg Ile Phe Gly His Pro Met
 355 360 365
 Val Asp Glu Arg Glu Ala Met Asp Ala Val Lys Leu Asn Asn Glu Ile
 370 375 380
 Thr Lys Ile Leu Lys Leu Glu Ser Leu Thr Glu Leu Arg Gly Ala Phe
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 405 410 415
 Lys Ile Lys Asn Leu Lys Val Leu Ser Lys Arg Trp Val Met Tyr Phe
 420 425 430
 Lys Ala Lys Ser Tyr Pro Ser Gln Leu Glu Leu Ser Val Gln Asp Phe
 435 440 445
 Leu Glu Leu Ala Ala Val Gln Phe Glu Gln Glu Phe Ser Val Pro Glu
 450 455 460
 Lys Thr Asn Leu Glu Met Val Leu Asn Asp Lys Ala Ile Ser Pro Pro
 465 470 475 480
 Lys Lys Leu Ile Trp Ser Val Tyr Pro Lys Asn Tyr Leu Pro Glu Ile
 485 490 495
 Ile Lys Asn Gln Tyr Leu Glu Glu Val Phe Asn Ala Ser Asp Ser Gln
 500 505 510
 Arg Thr Arg Arg Val Leu Glu Phe Tyr Leu Lys Asp Cys Lys Phe Asp
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 580 585 590
 Thr Leu Thr Lys Tyr Gly Asp Leu Asp Leu Gln Arg Ile Met Glu Met
 595 600 605
 Lys Ser Glu Leu Ser Ser Ile Lys Thr Arg Lys Asn Asp Ser Tyr Asn
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 Asn Tyr Ile Ala Arg Ala Ser Ile Val Thr Asp Leu Ser Lys Phe Asn
 625 630 635 640
 Gln Ala Phe Arg Tyr Glu Thr Thr Ala Ile Cys Ala Asp Val Ala Asp
 645 650 655
 Glu Leu His Gly Thr Gln Ser Leu Phe Cys Trp Leu His Leu Ile Val
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 Pro Met Thr Thr Met Ile Cys Ala Tyr Arg His Ala Pro Pro Glu Thr
 675 680 685
 Lys Gly Glu Tyr Asp Ile Asp Lys Ile Glu Glu Gln Ser Gly Leu Tyr
 690 695 700

Arg Tyr His Met Gly Gly Ile Glu Gly Trp Cys Gln Lys Leu Trp Thr
 705 710 715 720
 Met Glu Ala Ile Ser Leu Leu Asp Val Val Ser Val Lys Thr Arg Cys
 725 730 735
 Gln Met Thr Ser Leu Leu Asn Gly Asp Asn Gln Ser Ile Asp Val Ser
 740 745 750
 Lys Pro Val Lys Leu Ser Glu Gly Ile Asp Glu Val Lys Ala Asp Tyr
 755 760 765
 Ser Leu Ala Ile Lys Met Leu Lys Glu Ile Arg Asp Ala Tyr Lys Asn
 770 775 780
 Ile Gly His Lys Leu Lys Glu Gly Glu Thr Tyr Ile Ser Arg Asp Leu
 785 790 795 800
 Gln Phe Ile Ser Lys Val Ile Gln Ser Glu Gly Val Met His Pro Thr
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 Pro Ile Lys Lys Ile Leu Arg Val Gly Pro Trp Ile Asn Thr Ile Leu
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 Asp Asp Ile Lys Thr Ser Ala Glu Ser Ile Gly Ser Leu Cys Gln Glu
 835 840 845
 Leu Glu Phe Arg Gly Glu Ser Met Leu Val Ser Leu Ile Leu Arg Asn
 850 855 860
 Phe Trp Leu Tyr Asn Leu Tyr Met His Glu Ser Lys Gln His Pro Leu
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 Ala Gly Lys Gln Leu Phe Lys Gln Leu Asn Lys Thr Leu Thr Ser Val
 885 890 895
 Gln Arg Phe Phe Leu Lys Lys Glu Asn Asp Val Val Asp Leu Trp
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 980 985 990
 Arg Gln Ala Lys Val Thr Ser Asp Ile Asn Arg Thr Ala Val Thr Ser
 995 1000 1005
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 Pro Val Tyr Pro His Gly Leu Arg Val Leu Tyr Glu Ser Leu Pro Phe
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 Thr Asn Leu Leu Gln Arg Thr Ser Ala Ile Asn Gly Glu Asp Ile Asp
 1075 1080 1085
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 1090 1095 1100
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 Arg Leu Ile Cys Cys Gln Ile Ser Lys Thr Leu Arg Glu Lys Ser Trp
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 Met Asp Val Val Tyr Ala Thr Ser Ser His Leu Lys Gly Ile Ile Ile
 1155 1160 1165
 Glu Lys Phe Ser Thr Asp Lys Thr Thr Arg Gly Gln Arg Gly Pro Lys
 1170 1175 1180
 Ser Pro Trp Val Gly Ser Ser Thr Gln Glu Lys Lys Leu Val Pro Val
 1185 1190 1195 1200

Tyr Asn Arg Gln Ile Leu Ser Lys Gln Gln Lys Glu Gln Leu Glu Ala
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 1220 1225 1230
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 1235 1240 1245
 Val Lys Pro Leu Leu Pro Arg Phe Met Ser Val Asn Phe Leu His Arg
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 1265 1270 1275 1280
 Tyr Arg Thr Thr Asn Tyr His Phe Asp Thr Ser Pro Ile Asn Gln Ala
 1285 1290 1295
 Leu Ser Glu Arg Phe Gly Asn Glu Asp Ile Asn Leu Val Phe Gln Asn
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 Gly Arg Ser Pro Lys Gln Leu Val Leu Ile Pro Gln Leu Glu Glu Ile
 1330 1335 1340
 Asp Ile Met Pro Pro Val Phe Gln Gly Lys Phe Asn Tyr Lys Leu
 1345 1350 1355 1360
 Val Asp Lys Ile Thr Ser Asp Gln His Ile Phe Ser Pro Asp Lys Ile
 1365 1370 1375
 Asp Ile Leu Thr Leu Gly Lys Met Leu Met Pro Thr Ile Lys Gln
 1380 1385 1390
 Lys Thr Asp Gln Phe Leu Asn Lys Arg Glu Asn Tyr Phe His Gly Asn
 1395 1400 1405
 Asn Leu Ile Glu Ser Leu Ser Ala Ala Leu Ala Cys His Trp Cys Gly
 1410 1415 1420
 Ile Leu Thr Glu Gln Cys Val Glu Asn Asn Ile Phe Arg Lys Asp Trp
 1425 1430 1435 1440
 Gly Asp Gly Phe Ile Ser Asp His Ala Phe Met Asp Phe Lys Ile Phe
 1445 1450 1455
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 1475 1480 1485
 Leu Arg Ile Asp Asn Thr Phe Trp Arg Met Phe Ser Lys Val Met Phe
 1490 1495 1500
 Glu Ser Lys Val Lys Lys Arg Ile Met Leu Tyr Asp Val Lys Phe Leu
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 Ser Leu Val Gly Tyr Ile Gly Phe Lys Asn Trp Phe Ile Glu Gln Leu
 1525 1530 1535
 Arg Val Val Glu Leu His Glu Val Pro Trp Ile Val Asn Ala Glu Gly
 1540 1545 1550
 Glu Leu Val Glu Ile Lys Pro Ile Lys Ile Tyr Leu Gln Leu Ile Glu
 1555 1560 1565
 Gln Ser Leu Ser Leu Arg Ile Thr Val Leu Asn Tyr Thr Asp Met Ala
 1570 1575 1580
 His Ala Leu Thr Arg Leu Ile Arg Lys Lys Leu Met Cys Asp Asn Ala
 1585 1590 1595 1600
 Leu Phe Asn Pro Ser Ser Ser Pro Met Phe Ser Leu Thr Gln Val Ile
 1605 1610 1615
 Asp Pro Thr Thr Gln Leu Asp Tyr Phe Pro Lys Val Ile Phe Glu Arg
 1620 1625 1630
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 1635 1640 1645
 Arg Asn Tyr Met Thr Leu Leu Pro Trp Gln His Val Asn Arg Tyr Asn
 1650 1655 1660
 Phe Val Phe Ser Ser Thr Gly Cys Lys Ile Ser Leu Lys Thr Cys Ile
 1665 1670 1675 1680
 Gly Lys Leu Ile Lys Asp Leu Asn Pro Lys Val Leu Tyr Phe Ile Gly
 1685 1690 1695

Glu Gly Ala Gly Asn Trp Met Ala Arg Thr Ala Cys Glu Tyr Pro Asp
 1700 1705 1710
 Ile Lys Phe Val Tyr Arg Ser Leu Lys Asp Asp Leu Asp His His Tyr
 1715 1720 1725
 Pro Leu Glu Tyr Gln Arg Val Ile Gly Asp Leu Asn Arg Val Ile Asp
 1730 1735 1740
 Gly Gly Glu Gly Leu Ser Met Glu Thr Thr Asp Ala Thr Gln Lys Thr
 1745 1750 1755 1760
 His Trp Asp Leu Ile His Arg Ile Ser Lys Asp Ala Leu Leu Ile Thr
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 1780 1785 1790
 Ile Leu Trp Arg Lys His Val Leu Ser Cys Arg Ile Cys Thr Ala Tyr
 1795 1800 1805
 Gly Thr Asp Leu Tyr Leu Phe Ala Lys Tyr His Ala Thr Asp Cys Asn
 1810 1815 1820
 Ile Lys Leu Pro Phe Val Arg Ser Val Ala Thr Phe Ile Met Gln
 1825 1830 1835 1840
 Gly Ser Lys Leu Ser Gly Ser Glu Cys Tyr Ile Leu Leu Thr Leu Gly
 1845 1850 1855
 His His Asn Asn Leu Pro Cys His Gly Glu Ile Gln Asn Ser Lys Met
 1860 1865 1870
 Arg Ile Ala Val Cys Asn Asp Phe His Ala Ser Lys Lys Leu Asp Asn
 1875 1880 1885
 Lys Ser Ile Glu Ala Asn Cys Lys Ser Leu Leu Ser Gly Leu Arg Ile
 1890 1895 1900
 Pro Ile Asn Lys Lys Glu Leu Asn Arg Gln Lys Lys Leu Leu Thr Leu
 1905 1910 1915 1920
 Gln Ser Asn His Ser Ser Ile Ala Thr Val Gly Gly Ser Lys Ile Ile
 1925 1930 1935
 Glu Ser Lys Trp Leu Lys Asn Lys Ala Ser Thr Ile Ile Asp Trp Leu
 1940 1945 1950
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 1955 1960 1965
 Glu Ala Leu Glu Asn Thr Tyr Pro Asn Met Ile Lys Leu Ile Asp Asn
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<210> 42
 <211> 187
 <212> PRT
 <213> human Metapneumo virus

<400> 42
 Met Ser Arg Lys Ala Pro Cys Lys Tyr Glu Val Arg Gly Lys Cys Asn
 1 5 10 15
 Arg Gly Ser Glu Cys Lys Phe Asn His Asn Tyr Trp Ser Trp Pro Asp
 20 25 30
 Arg Tyr Leu Leu Ile Arg Ser Asn Tyr Leu Leu Asn Gln Leu Leu Arg
 35 40 45
 Asn Thr Asp Arg Ala Asp Gly Leu Ser Ile Ile Ser Gly Ala Gly Arg
 50 55 60

Glu Asp Arg Thr Gln Asp Phe Val Leu Gly Ser Thr Asn Val Val Gln
 65 70 75 80
 Gly Tyr Ile Asp Asp Asn Gln Ser Ile Thr Lys Ala Ala Ala Cys Tyr
 85 90 95
 Ser Leu His Asn Ile Ile Lys Gln Leu Gln Glu Val Glu Val Arg Gln
 100 105 110
 Ala Arg Asp Asn Lys Leu Ser Asp Ser Lys His Val Ala Leu His Asn
 115 120 125
 Leu Val Leu Ser Tyr Met Glu Met Ser Lys Thr Pro Ala Ser Leu Ile
 130 135 140
 Asn Asn Leu Lys Arg Leu Pro Arg Glu Lys Leu Lys Lys Leu Ala Lys
 145 150 155 160
 Leu Ile Ile Asp Leu Ser Ala Gly Ala Glu Asn Asp Ser Ser Tyr Ala
 165 170 175
 Leu Gln Asp Ser Glu Ser Thr Asn Gln Val Gln
 180 185

<210> 43
 <211> 187
 <212> PRT
 <213> human Metapneumo virus

<400> 43
 Met Ser Arg Lys Ala Pro Cys Lys Tyr Glu Val Arg Gly Lys Cys Asn
 1 5 10 15
 Arg Gly Ser Glu Cys Lys Phe Asn His Asn Tyr Trp Ser Trp Pro Asp
 20 25 30
 Arg Tyr Leu Leu Ile Arg Ser Asn Tyr Leu Leu Asn Gln Leu Leu Arg
 35 40 45
 Asn Thr Asp Arg Ala Asp Gly Leu Ser Ile Ile Ser Gly Ala Gly Arg
 50 55 60
 Glu Asp Arg Thr Gln Asp Phe Val Leu Gly Ser Thr Asn Val Val Gln
 65 70 75 80
 Gly Tyr Ile Asp Asp Asn Gln Ser Ile Thr Lys Ala Ala Ala Cys Tyr
 85 90 95
 Ser Leu His Asn Ile Ile Lys Gln Leu Gln Glu Val Glu Val Arg Gln
 100 105 110
 Ala Arg Asp Ser Lys Leu Ser Asp Ser Lys His Val Ala Leu His Asn
 115 120 125
 Leu Ile Leu Ser Tyr Met Glu Met Ser Lys Thr Pro Ala Ser Leu Ile
 130 135 140
 Asn Asn Leu Lys Arg Leu Pro Arg Glu Lys Leu Lys Lys Leu Ala Lys
 145 150 155 160
 Leu Ile Ile Asp Leu Ser Ala Gly Ala Asp Asn Asp Ser Ser Tyr Ala
 165 170 175
 Leu Gln Asp Ser Glu Ser Thr Asn Gln Val Gln
 180 185

<210> 44
 <211> 187
 <212> PRT
 <213> human Metapneumo virus

<400> 44
 Met Ser Arg Lys Ala Pro Cys Lys Tyr Glu Val Arg Gly Lys Cys Asn
 1 5 10 15
 Arg Gly Ser Asp Cys Lys Phe Asn His Asn Tyr Trp Ser Trp Pro Asp
 20 25 30
 Arg Tyr Leu Leu Leu Arg Ser Asn Tyr Leu Leu Asn Gln Leu Leu Arg
 35 40 45

Asn Thr Asp Lys Ala Asp Gly Leu Ser Ile Ile Ser Gly Ala Gly Arg
 50 55 60
 Glu Asp Arg Thr Gln Asp Phe Val Leu Gly Ser Thr Asn Val Val Gln
 65 70 75 80

 Gly Tyr Ile Asp Asp Asn Gln Gly Ile Thr Lys Ala Ala Ala Cys Tyr
 85 90 95
 Ser Leu His Asn Ile Ile Lys Gln Leu Gln Glu Thr Glu Val Arg Gln
 100 105 110
 Ala Arg Asp Asn Lys Leu Ser Asp Ser Lys His Val Ala Leu His Asn
 115 120 125
 Leu Ile Leu Ser Tyr Met Glu Met Ser Lys Thr Pro Ala Ser Leu Ile
 130 135 140
 Asn Asn Leu Lys Lys Leu Pro Arg Glu Lys Leu Lys Lys Leu Ala Arg
 145 150 155 160
 Leu Ile Ile Asp Leu Ser Ala Gly Thr Asp Asn Asp Ser Ser Tyr Ala
 165 170 175
 Leu Gln Asp Ser Glu Ser Thr Asn Gln Val Gln
 180 185

<210> 45
 <211> 187
 <212> PRT
 <213> human Metapneumo virus

<400> 45
 Met Ser Arg Lys Ala Pro Cys Lys Tyr Glu Val Arg Gly Lys Cys Asn
 1 5 10 15
 Arg Gly Ser Glu Cys Lys Phe Asn His Asn Tyr Trp Ser Trp Pro Asp
 20 25 30
 Arg Tyr Leu Leu Leu Arg Ser Asn Tyr Leu Leu Asn Gln Leu Leu Arg
 35 40 45
 Asn Thr Asp Lys Ala Asp Gly Leu Ser Ile Ile Ser Gly Ala Gly Arg
 50 55 60
 Glu Asp Arg Thr Gln Asp Phe Val Leu Gly Ser Thr Asn Val Val Gln
 65 70 75 80
 Gly Tyr Ile Asp Asn Asn Gln Gly Ile Thr Lys Ala Ala Ala Cys Tyr
 85 90 95
 Ser Leu His Asn Ile Ile Lys Gln Leu Gln Glu Ile Glu Val Arg Gln
 100 105 110
 Ala Arg Asp Asn Lys Leu Ser Asp Ser Lys His Val Ala Leu His Asn
 115 120 125
 Leu Ile Leu Ser Tyr Met Glu Met Ser Lys Thr Pro Ala Ser Leu Ile
 130 135 140
 Asn Asn Leu Lys Lys Leu Pro Arg Glu Lys Leu Lys Lys Leu Ala Lys
 145 150 155 160
 Leu Ile Ile Asp Leu Ser Ala Gly Thr Asp Asn Asp Ser Ser Tyr Ala
 165 170 175
 Leu Gln Asp Ser Glu Ser Thr Asn Gln Val Gln
 180 185

<210> 46
 <211> 564
 <212> DNA
 <213> human Metapneumo virus

<400> 46
 atgtctcgca aggctccgtg caaatatgaa gtgcggggca aatgcaatag aggaagttag 60
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 tatttattaa atcaactttt aaggaacact gatagagctg atggcttatac aataatatca 180

ggagcaggca gagaagatag gacacaagat tttgtcctag gttccaccaa tgtggttcaa 240
 gtttatattg atgataacca aagcataaca aaagctgcag cctgttacag tctacataat 300
 ataatcaaac aactacaaga agttgaagtt aggcaggcta gagataacaa actatctgac 360
 agcaaacatg tagcacttca caacttagtc ctatcttata tggagatgag caaaaactcct 420
 gcatcttta tcaacaatct caagagactg ccgagagaga aactaaaaaa attagcaaag 480
 ctcataattg acttatacgc aggtgctgaa aatgactctt catatgcctt gcaagacagt 540
 gaaagcacta atcaagtgcgt 564

<210> 47
 <211> 564
 <212> DNA
 <213> human Metapneumo virus

<400> 47
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 tatctttaat atcagctttt aaggaacact gataaggctg atggcctatc aataatatca 180
 ggccgaggca gagaagacag aacgcacat tttgttctag gttccaccaa tgtggttcaa 240
 ggttatattg atgataacca aagcataaca aaagctgcag cctgttacag tctacacaac 300
 ataatcaagc aactacaaga agttgaagtt aggcaggcta gagataacaa actatctgac 360
 agcaagcatg tggcactcca taacttaatc ttatcttaca tggagatgag caaaaactccc 420
 gcatcttta tcaacaatct taaaagactg ccgagagaaaa aactaaaaaa attagcaaag 480
 ctgataattg acttatacgc aggcgctgac aatgactctt catatgcctt gcaagacagt 540
 gaaagcacta atcaagtgcgt 564

<210> 48
 <211> 564
 <212> DNA
 <213> human Metapneumo virus

<400> 48
 atgtctcgta aggctccatg caaatatgaa gtgcggggca aatgcaacag agggagtgat 60
 tgcaatttca atcacaatta ctggagttgg cctgtatagat atttattttt aagatcaaat 120
 tatctttaat atcagctttt aagaaacaca gataaggctg atggtttgc aataatatca 180
 ggagcaggta gagaagatag aactcaagac tttgttcttg gttctactaa tgtggttcaa 240
 gggtacattt atgacaacca aggaataacc aaggctgcag cttgtttagt tctacacaac 300
 ataatcaagc aactacaaga aacagaagta agacaggcta gagacaacaa gctttctgat 360
 agcaaacatg tggcgttcca caacttgata ttatcttata tggagatgag caaaaactcct 420
 gcatctctaa tcaacaacctt aaagaaacta ccaagggaaa aactgaagaa attagcaaga 480
 ttaataattt atttatacgc aggaactgac aatgactctt catatgcctt gcaagacagt 540
 gaaagcacta atcaagtgcgt 564

<210> 49
 <211> 564
 <212> DNA
 <213> human Metapneumo virus

<400> 49
 atgtctcgca aagctccatg caaatatgaa gtacggggca agtgcaacag gggaaagttag 60
 tgcaatttca accacaatta ctggagctgg cctgtataggt atttattttt aagatcaaat 120
 tatctttaat atcagctttt aagaaacact gataaggctg atggtttgc aataatatca 180
 ggagcaggta gagaagatag gactcaagac tttgttcttg gttctactaa tgtggttcaa 240
 gggtacattt ataacaatca aggaataacc aaggctgcag cttgtttagt tctacataac 300
 ataataaaac agctacaaga aatagaagta agacaggcta gagataataa gctttctgac 360
 agcaaacatg tggcacttca caacttgata ttatcttata tggagatgag caaaaactcct 420
 gcatccctga ttaataacctt aaagaaacta ccaagagaaaa aactgaagaa attagcgaaa 480
 ttaataattt atttatacgc aggaactgat aatgactctt catatgcctt gcaagacagt 540
 gaaagcacta atcaagtgcgt 564

<210> 50
 <211> 71
 <212> PRT

<213> human Metapneumo virus

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<400> 50
Met Thr Leu His Met Pro Cys Lys Thr Val Lys Ala Leu Ile Lys Cys
      5          10          15
Ser Glu His Gly Pro Val Phe Ile Thr Ile Glu Val Asp Asp Met Ile
      20          25          30
Trp Thr His Lys Asp Leu Lys Glu Ala Leu Ser Asp Gly Ile Val Lys
      35          40          45
Ser His Thr Asn Ile Tyr Asn Cys Tyr Leu Glu Asn Ile Glu Ile Ile
      50          55          60
Tyr Val Lys Ala Tyr Leu Ser
65          70

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<210> 51

<211> 71

<212> PRT

<213> human Metapneumo virus

<400> 51

<210> 52

<211> 71

<212> PRT

<213> human Metapneumo virus

<400> 52

<210> 53

<211> 71

<212> PRT

<213> human Metapneumo virus

<400> 53

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Met Thr Leu His Met Pro Cys Lys Thr Val Lys Ala Leu Ile Lys Cys
      1          5          10         15
Ser Lys His Gly Pro Lys Phe Ile Thr Ile Glu Ala Asp Asp Met Ile
      20          25         30
Trp Thr His Lys Glu Leu Lys Glu Thr Leu Ser Asp Gly Ile Val Lys

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35	40	45
Ser His Thr Asn Ile Tyr Ser Cys Tyr Leu Glu Asn Ile Glu Ile Ile		
50	55	60
Tyr Val Lys Ala Tyr Leu Ser		
65	70	

<210> 54
<211> 216
<212> DNA
<213> human Metapneumo virus

<400> 54
atgactcttc atatgccttg caagacagtg aaagcactaa tcaagtgcag tgagcatgg 60
ccagtttca ttactataga ggttgatgac atgatatgg ctcacaagg cttaaaagaa 120
gctttatctg atggatagt gaagtctcat actaacattt acaatttgtt ttttagaaaac 180
atagaaatta tatatgtcaa ggcttactta agttag 216

<210> 55
<211> 216
<212> DNA
<213> human Metapneumo virus

<400> 55
atgactcttc atatgccctg caagacagtg aaagcactaa tcaagtgcag tgagcatgg 60
cctgtttca ttactataga ggttgatgaa atgatatgg ctcaaaaaga attaaaagaa 120
gcttgcccg atggatagt gaagtctcac accaacattt acaatttgtt ttttagaaaac 180
atagaaatta tatatgtcaa ggcttactta agttag 216

<210> 56
<211> 216
<212> DNA
<213> human Metapneumo virus

<400> 56
atgactcttc atatgccttg caagacagtg aaagcactaa tcaagtgcag taaacatgg 60
cccaaattca ttaccataga ggcagatgtat atgatatgg ctcacaagg attaaaagaa 120
acactgtctg atggatagt aaaatcacac accaatattt atagtttgtt ctttagaaaat 180
atagaaataa tatatgttaa aacttactta agttag 216

<210> 57
<211> 216
<212> DNA
<213> human Metapneumo virus

<400> 57
atgactcttc atatgccttg caagacagtg aaagcactaa tcaagtgcag taagcatgg 60
cccaaattca ttaccataga ggcagatgtat atgatatgg cacacaagg attaaaggag 120
acactgtctg atggatagt aaaatcacac accaatattt acagtttgtt ttttagaaaat 180
atagaaataa tatatgttaa agcttactta agttag 216

<210> 58
<211> 727
<212> DNA
<213> human Metapneumo virus

<400> 58
atgtctcgca aggctccgtg caaatatgaa gtgcggggca aatgcaatag aggaagttag 60
tgcaagtttta accacaattt ctggagttgg ccagatagat acttattaat aagatcaa 120
tatttattaa atcaactttt aaggaacact gatagagctg atggcttatac aataatata 180
ggagcaggca gagaagatag gacacaagat tttgtcctag gttccaccaa tgtggttcaa 240
ggtttatattt atgataacca aagcataaca aaagctgcag cctgttacag tctacataat 300

ataatcaaac aactacaaga agttgaagtt aggaggcta gagataacaa actatctgac 360
 agcaaacatg tagcaattca caacttagtc ctatcttata tggagatgag caaaaactcct 420
 gcatcttaa tcaacaatct caagagactg ccgagagaga aactaaaaaa attagcaaag 480
 ctcataattg acttatcagc aggtgctgaa aatgactctt catatgcctt gcaagacagt 540
 gaaagcacta atcaagtgc a gtgagcatgg tcctgtttc attactatag agttgatga 600
 catgatatgg actcacaagg actaaaaaga agctttatct gatggatag tgaagtctca 660
 tactaacatt tacaattgtt atttagaaaaa catagaaatt atatatgtca aggcttactt 720
 aagttag 727

<210> 59
<211> 727
<212> DNA
<213> human Metapneumo virus

<400> 59
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 tatctttaa atcagcttt aaggaacact gataaggctg atggccatc aataatatca 180
 ggccaggca gagaagacag aacgcaagat tttgttctag gttccaccaa tgggttcaa 240
 gtttataatg atgataacca aagcataaca aaagctgcag cctgctacag tctacacaac 300
 ataatcaagc aactacaaga agttgaagtt aggaggcta gagatagcaa actatctgac 360
 agcaagcatg tggcaactca taacttaatc ttatcttaca tggagatgag caaaaactccc 420
 gcatcttaa tcaacaatct taaaagactg ccgagagaaa aactaaaaaa attagcaaag 480
 ctgataatg acttatcagc aggctgcgtac aatgactctt catatgcctt gcaagacagt 540
 gaaagcacta atcaagtgc a gtgagcatgg tcctgtttc attactatag agttgatga 600
 atgatatgg actcacaagg aattaaaaga agctttgtcc gatggatag tgaagtctca 660
 caccaacatt tacaattgtt atttagaaaaa catagaaatt atatatgtca aggcttactt 720
 aagttag 727

<210> 60
<211> 727
<212> DNA
<213> human Metapneumo virus

<400> 60
 atgtctcgta aggctccatg ccaaataatgaa gtgcggggca aatgcaacag agggagtgtat 60
 tgcaaaattca atcacaatta ctggagttgg cctgatagat atttattgtt aagatcaaat 120
 tatctcttaa atcagcttt aagaaacaca gataaggctg atggttgtc aataatatca 180
 ggagcaggtt gagaagatag aactcaagac tttgttcttg gttctactaa tgggttcaa 240
 gggtacatg atgacaacca aggaataacc aaggctgcag cttgctatag tctacacaac 300
 ataatcaagc aactacaaga aacagaagta agacaggcta gagacaacaa gcttctgat 360
 agcaaacatg tggcgttcca caacttgata ttatcctata tggagatgag caaaaactcct 420
 gcatctctaa tcaacaacct aaagaaacta ccaaggggaaa aactgaagaa attagcaaga 480
 ttaataatg atttatcagc aggaactgac aatgactctt catatgcctt gcaagacagt 540
 gaaagcacta atcaagtgc a gtaaacatgg tcctaaattc attaccatag aggcatgat 600
 tatgatatgg actcacaagg aattaaaaga aacactgtct gatggatag taaaatcaca 660
 caccaatatt tataattgtt acttagaaaaa tatagaaata atatatgtta aaacttactt 720
 aagttag 727

<210> 61
<211> 727
<212> DNA
<213> human Metapneumo virus

<400> 61
 atgtctcgca aagctccatg ccaaataatgaa gtacggggca agtgcaacag gggaaagttag 60
 tgcaaaattca accacaatta ctggagctgg cctgataggt atttattgtt aagatcaaat 120
 tatctcttga atcagcttt aagaaacact gataaggctg atggttgtc aataatatca 180
 ggagcaggtt gagaagatag gactcaagac tttgttcttg gttctactaa tgggttcaa 240
 gggtacatg ataacaatca aggaataaca aaggctgcag cttgctatag tctacataac 300
 ataataaaac agctacaaga aatagaagta agacaggcta gagataataa gcttctgac 360
 agcaaacatg tggcaattca caacttgata ttatcctata tggagatgag caaaaactcct 420

gcatccctga ttaataacct aaagaaaacta ccaagagaaaa aactgaagaa attagcgaaa 480
 ttaataattt gtttatcagc aggaactgat aatgactctt catatgcctt gcaagacagt 540
 gaaaggacta atcaagtgcgtt gtaagcatgg tcccaaattt attaccatag aggcagatgtt 600
 tatgatatgg acacacaaag aattaaagga gacactgtct gatgggatgtt taatataatcaca 660
 caccaatatt tacagttgtt atttagaaaa tatagaaata atatatgtt aagcttactt 720
 aagtttag 727

<210> 62

<211> 254

<212> PRT

<213> human Metapneumo virus

<400> 62

Met	Glu	Ser	Tyr	Leu	Val	Asp	Thr	Tyr	Gln	Gly	Ile	Pro	Tyr	Thr	Ala
1									10						15
Ala	Val	Gln	Val	Asp	Leu	Ile	Glu	Lys	Asp	Leu	Leu	Pro	Ala	Ser	Leu
								20		25					30
Thr	Ile	Trp	Phe	Pro	Leu	Phe	Gln	Ala	Asn	Thr	Pro	Pro	Ala	Val	Leu
								35		40					45
Leu	Asp	Gln	Leu	Lys	Thr	Leu	Thr	Ile	Thr	Leu	Tyr	Ala	Ala	Ser	
								50		55					60
Gln	Asn	Gly	Pro	Ile	Leu	Lys	Val	Asn	Ala	Ser	Ala	Gln	Gly	Ala	Ala
								65		70		75			80
Met	Ser	Val	Leu	Pro	Lys	Lys	Phe	Glu	Val	Asn	Ala	Thr	Val	Ala	Leu
								85		90					95
Asp	Glu	Tyr	Ser	Lys	Leu	Glu	Phe	Asp	Lys	Leu	Thr	Val	Cys	Glu	Val
								100		105					110
Lys	Thr	Val	Tyr	Leu	Thr	Thr	Met	Lys	Pro	Tyr	Gly	Met	Val	Ser	Lys
								115		120					125
Phe	Val	Ser	Ser	Ala	Lys	Ser	Val	Gly	Lys	Lys	Thr	His	Asp	Leu	Ile
								130		135					140
Ala	Leu	Cys	Asp	Phe	Met	Asp	Leu	Glu	Lys	Asn	Thr	Pro	Val	Thr	Ile
								145		150		155			160
Pro	Ala	Phe	Ile	Lys	Ser	Val	Ser	Ile	Lys	Glu	Ser	Glu	Ser	Ala	Thr
								165		170					175
Val	Glu	Ala	Ala	Ile	Ser	Ser	Glu	Ala	Asp	Gln	Ala	Leu	Thr	Gln	Ala
								180		185					190
Lys	Ile	Ala	Pro	Tyr	Ala	Gly	Leu	Ile	Met	Ile	Met	Thr	Met	Asn	Asn
								195		200					205
Pro	Lys	Gly	Ile	Phe	Lys	Lys	Leu	Gly	Ala	Gly	Thr	Gln	Val	Ile	Val
								210		215					220
Glu	Leu	Gly	Ala	Tyr	Val	Gln	Ala	Glu	Ser	Ile	Ser	Lys	Ile	Cys	Lys
								225		230		235			240
Thr	Trp	Ser	His	Gln	Gly	Thr	Arg	Tyr	Val	Leu	Lys	Ser	Arg		
								245		250					

<210> 63

<211> 254

<212> PRT

<213> human Metapneumo virus

<400> 63

Met	Glu	Ser	Tyr	Leu	Val	Asp	Thr	Tyr	Gln	Gly	Ile	Pro	Tyr	Thr	Ala
1									10						15
Ala	Val	Gln	Val	Asp	Leu	Val	Glu	Lys	Asp	Leu	Leu	Pro	Ala	Ser	Leu
								20		25					30
Thr	Ile	Trp	Phe	Pro	Leu	Phe	Gln	Ala	Asn	Thr	Pro	Pro	Ala	Val	Leu
								35		40					45
Leu	Asp	Gln	Leu	Lys	Thr	Leu	Thr	Ile	Thr	Leu	Tyr	Ala	Ala	Ser	
								50		55					60
Gln	Ser	Gly	Pro	Ile	Leu	Lys	Val	Asn	Ala	Ser	Ala	Gln	Gly	Ala	Ala

65	70	75	80
Met Ser Val Leu Pro Lys Lys Phe Glu Val Asn Ala Thr Val Ala Leu			
85	90	95	
Asp Glu Tyr Ser Lys Leu Glu Phe Asp Lys Leu Thr Val Cys Glu Val			
100	105	110	
Lys Thr Val Tyr Leu Thr Thr Met Lys Pro Tyr Gly Met Val Ser Lys			
115	120	125	
Phe Val Ser Ser Ala Lys Ser Val Gly Lys Lys Thr His Asp Leu Ile			
130	135	140	
Ala Leu Cys Asp Phe Met Asp Leu Glu Lys Asn Thr Pro Val Thr Ile			
145	150	155	160
Pro Ala Phe Ile Lys Ser Val Ser Ile Lys Glu Ser Glu Ser Ala Thr			
165	170	175	
Val Glu Ala Ala Ile Ser Ser Glu Ala Asp Gln Ala Leu Thr Gln Ala			
180	185	190	
Lys Ile Ala Pro Tyr Ala Gly Leu Ile Met Ile Met Thr Met Asn Asn			
195	200	205	
Pro Lys Gly Ile Phe Lys Lys Leu Gly Ala Gly Thr Gln Val Ile Val			
210	215	220	
Glu Leu Gly Ala Tyr Val Gln Ala Glu Ser Ile Ser Lys Ile Cys Lys			
225	230	235	240
Thr Trp Ser His Gln Gly Thr Arg Tyr Val Leu Lys Ser Ser			
245	250		

<210> 64
<211> 254
<212> PRT
<213> human Metapneumo virus

<400> 64			
Met Glu Ser Tyr Leu Val Asp Thr Tyr Gln Gly Ile Pro Tyr Thr Ala			
1	5	10	15
Ala Val Gln Val Asp Leu Val Glu Lys Asp Leu Leu Pro Ala Ser Leu			
20	25	30	
Thr Ile Trp Phe Pro Leu Phe Gln Ala Asn Thr Pro Pro Ala Val Leu			
35	40	45	
Leu Asp Gln Leu Lys Thr Leu Thr Ile Thr Leu Tyr Ala Ala Ser			
50	55	60	
Gln Asn Gly Pro Ile Leu Lys Val Asn Ala Ser Ala Gln Gly Ala Ala			
65	70	75	80
Met Ser Val Leu Pro Lys Lys Phe Glu Val Asn Ala Thr Val Ala Leu			
85	90	95	
Asp Glu Tyr Ser Lys Leu Asp Phe Asp Lys Leu Thr Val Cys Asp Val			
100	105	110	
Lys Thr Val Tyr Leu Thr Thr Met Lys Pro Tyr Gly Met Val Ser Lys			
115	120	125	
Phe Val Ser Ser Ala Lys Ser Val Gly Lys Lys Thr His Asp Leu Ile			
130	135	140	
Ala Leu Cys Asp Phe Met Asp Leu Glu Lys Asn Ile Pro Val Thr Ile			
145	150	155	160
Pro Ala Phe Ile Lys Ser Val Ser Ile Lys Glu Ser Glu Ser Ala Thr			
165	170	175	
Val Glu Ala Ala Ile Ser Ser Glu Ala Asp Gln Ala Leu Thr Gln Ala			
180	185	190	
Lys Ile Ala Pro Tyr Ala Gly Leu Ile Met Ile Met Thr Met Asn Asn			
195	200	205	
Pro Lys Gly Ile Phe Lys Lys Leu Gly Ala Gly Thr Gln Val Ile Val			
210	215	220	
Glu Leu Gly Ala Tyr Val Gln Ala Glu Ser Ile Ser Arg Ile Cys Lys			
225	230	235	240
Ser Trp Ser His Gln Gly Thr Arg Tyr Val Leu Lys Ser Arg			

245

250

<210> 65
<211> 254
<212> PRT
<213> human Metapneumo virus

<400> 65
Met Glu Ser Tyr Leu Val Asp Thr Tyr Gln Gly Ile Pro Tyr Thr Ala
1 5 10 15
Ala Val Gln Val Asp Leu Val Glu Lys Asp Leu Leu Pro Ala Ser Leu
20 25 30
Thr Ile Trp Phe Pro Leu Phe Gln Ala Asn Thr Pro Pro Ala Val Leu
35 40 45
Leu Asp Gln Leu Lys Thr Leu Thr Ile Thr Leu Tyr Ala Ala Ser
50 55 60
Gln Asn Gly Pro Ile Leu Lys Val Asn Ala Ser Ala Gln Gly Ala Ala
65 70 75 80
Met Ser Val Leu Pro Lys Lys Phe Glu Val Asn Ala Thr Val Ala Leu
85 90 95
Asp Glu Tyr Ser Lys Leu Asp Phe Asp Lys Leu Thr Val Cys Asp Val
100 105 110
Lys Thr Val Tyr Leu Thr Thr Met Lys Pro Tyr Gly Met Val Ser Lys
115 120 125
Phe Val Ser Ser Ala Lys Ser Val Gly Lys Lys Thr His Asp Leu Ile
130 135 140
Ala Leu Cys Asp Phe Met Asp Leu Glu Lys Asn Ile Pro Val Thr Ile
145 150 155 160
Pro Ala Phe Ile Lys Ser Val Ser Ile Lys Glu Ser Glu Ser Ala Thr
165 170 175
Val Glu Ala Ala Ile Ser Ser Glu Ala Asp Gln Ala Leu Thr Gln Ala
180 185 190
Lys Ile Ala Pro Tyr Ala Gly Leu Ile Met Ile Met Thr Met Asn Asn
195 200 205
Pro Lys Gly Ile Phe Lys Lys Leu Gly Ala Gly Thr Gln Val Ile Val
210 215 220
Glu Leu Gly Ala Tyr Val Gln Ala Glu Ser Ile Ser Arg Ile Cys Lys
225 230 235 240
Ser Trp Ser His Gln Gly Thr Arg Tyr Val Leu Lys Ser Arg
245 250

<210> 66
<211> 765
<212> DNA
<213> human Metapneumo virus

<400> 66
atggagtctt accttagtaga caccttatcaa ggcatttcctt acacagcagc tggcaagg 60
gatctaatacg aaaaggaccc ttacactgca agcctaaca tatggttccc ttgttttcag 120
gccaacacac caccacgact gctgctcgat cagctaaaaa ccctgacaat aaccactctg 180
tatgctgcat cacaaaatgg tccaataactc aaagtgaatg catcagcccc aggtgcagca 240
atgtctgtac ttcccaaaaa atttgaagtc aatgcgactg tagcactcga tgaatatagc 300
aaactggaat ttgacaaact cacagtctgt gaagtaaaaa cagtttactt aacaaccatg 360
aaaccatacg ggatggtatac aaaatttttg agtcagcca aatcagggttgg caaaaaaaca 420
catgatctaa tcgactatg tgatttatg gatctagaaa agaacacacc tggtaataata 480
ccagcattca tcaaatcagt ttcaatcaaa gagagtgagt cagctactgt tgaagctgct 540
ataaggcagt aagcagacca agctctaaca caggccaaaa ttgcacccca tgcgggatta 600
attatgatca tgactatgaa caatccaaa ggcatttca aaaagcttgg agctgggact 660
caagtcatag tagaacttagg agcatatgtc caggctgaaa gcataagcaa aatatgcaag 720
acttggagcc atcaagggac aagatatgtc ttgaagtcca gataa 765

<210> 67
<211> 765
<212> DNA
<213> human Metapneumo virus

<400> 67
atggagtctt atctggtaga cacttatcaa ggcattccctt acacagcagc tttcaagtt 60
gatcttagtag aaaaggacct gttacctgca agcttaacaa tatggttccc ctgtttcag 120
gccaacacac caccagcagt tctgttgat cagctaaaaga ctctgactat aactactcg 180
tatgtctgcat cacaaagtgg tccaaatacta aaagtgaatg catcagccca gggtcagca 240
atgtctgtac ttcccaaaaa gtttgaagtc aatgcgactg tagcacttga cgaatatacg 300
aaatttagaat ttgacaaact tacagtcgt gaagtaaaaaa cagtttactt aacaaccatg 360
aaaccatatg ggatggtataa aagtttgat agtcggcca aatcagttgg caaaaaaaca 420
catgtcttaa tcgcattatg tgatttatg gatctagaaa agaacacacc agttacaata 480
ccagcattta tcaaatacgat ttctatcaag gagagtgaat cagccactgt tgaagctgca 540
ataagcagtg aagcagacca agctctaaca caagccaaaa ttgcaccta tgcgggactg 600
atcatgatca tgaccatgaa caatccaaaa ggcattattca agaagcttgg agctgggacc 660
caagttatacg tagaacttagg agcatatgtc caggctgaaa gcataagtaa aatatgcaag 720
acttggagcc atcaaggaac aagatatgtc ctgaagtc gttaa 765

<210> 68
<211> 765
<212> DNA
<213> human Metapneumo virus

<400> 68
atggagtctt atcttagtata cacttatcaa ggcattccat atacagctgc tttcaagtt 60
gacctggtag aaaaagattt actgccagca agtttgcacaa tatggttcc ttatattcag 120
gccaacacac caccagcagt tctgttgat cagctaaaaga cttgacaat aacaactctg 180
tatgtctgcat cacaaatgg tccaaatactc aaggtaaatg catctgccc aggtgctgca 240
atgtctgtac ttcccaaaaa attcgaggtt aatgcactg tagcacttga tgaatacagt 300
aaacttggatt ttgacaagct gacggcttgc gatgttaaaa cagtttattt gacaactatg 360
aaaccgtacg ggatggtgc aaaaattttg agttcagcca aatcagttgg caaaaagaca 420
catgtcttaa ttgcactatg tgacttcatg gacctagaga aaaaataacc tggacaata 480
ccagcattca taaagtcatg ttcaatcaaa gagagtgaat cagccactgt tgaagctgca 540
ataagcagcg aagccgacca agccttgaca caagccaga ttgcgccta tgcaggacta 600
attatgatca tgaccatgaa caatccaaaa ggtatattca agaaacttagg ggctggaca 660
caagttatacg tagagctggg ggcataatgtt caggctgaga gcatcgttag gatctgcaag 720
agcttggatgc accaaggaac aagatatacgta ctaaaatcca gataa 765

<210> 69
<211> 765
<212> DNA
<213> human Metapneumo virus

<400> 69
atggagtctt atcttagtgaa cacttatcaa ggcattccctt acacagctgc tttcaagtt 60
gatctggtag aaaaagactt actaccagca agtttgcacaa tatggttcc tctattccaa 120
gccaacacac caccagcggt tttgtctgat cagctaaaaga cttgactat aacaactctg 180
tatgtctgcat cacaaatgg tccaaatactc aaggtaaatg catcagctca gggctgtgt 240
atgtctgtac ttcccaaaaa attcgaggtt aatgcactg tggcacttga tgaatacagc 300
aaacttggact ttgacaagtt aacggttgc gatgttaaaa cagtttattt gacaaccatg 360
aagccatatg ggatggtgc aaaaattttg agttcagcca aatcagttgg caaaaagaca 420
catgtcttaa ttgcactgtg tgacttcatg gacctagaga aaaaataacc tggacaata 480
ccagcattca taaagtcatg ttcaatcaaa gagagtgtgt cagccactgt tgaagctgca 540
ataagcagtg aggccgacca agcattaaca caagccaaaa ttgcaccta tgcaggacta 600
atcatgatca tgaccatgaa caatccaaaa ggtatattca agaaacttagg agctggaca 660
caagttatacg tagagctggg ggcataatgtt caagccgaga gcatcgttag gatctgcaag 720
agcttggatgc accaaggaac aagatatacgta ctaaaatcca gataa 765

<210> 70
<211> 394

<212> PRT

<213> human Metapneumo virus

<400> 70

Met Ser Leu Gln Gly Ile His Leu Ser Asp Leu Ser Tyr Lys His Ala
 1 5 10 15
 Ile Leu Lys Glu Ser Gln Tyr Thr Ile Lys Arg Asp Val Gly Thr Thr
 20 25 30
 Thr Ala Val Thr Pro Ser Ser Leu Gln Gln Glu Ile Thr Leu Leu Cys
 35 40 45
 Gly Glu Ile Leu Tyr Ala Lys His Ala Asp Tyr Lys Tyr Ala Ala Glu
 50 55 60
 Ile Gly Ile Gln Tyr Ile Ser Thr Ala Leu Gly Ser Glu Arg Val Gln
 65 70 75 80
 Gln Ile Leu Arg Asn Ser Gly Ser Glu Val Gln Val Val Leu Thr Arg
 85 90 95
 Thr Tyr Ser Leu Gly Lys Ile Lys Asn Asn Lys Gly Glu Asp Leu Gln
 100 105 110
 Met Leu Asp Ile His Gly Val Glu Lys Ser Trp Val Glu Glu Ile Asp
 115 120 125
 Lys Glu Ala Arg Lys Thr Met Ala Thr Leu Leu Lys Glu Ser Ser Gly
 130 135 140
 Asn Ile Pro Gln Asn Gln Arg Pro Ser Ala Pro Asp Thr Pro Ile Ile
 145 150 155 160
 Leu Leu Cys Val Gly Ala Leu Ile Phe Thr Lys Leu Ala Ser Thr Ile
 165 170 175
 Glu Val Gly Leu Glu Thr Thr Val Arg Arg Ala Asn Arg Val Leu Ser
 180 185 190
 Asp Ala Leu Lys Arg Tyr Pro Arg Met Asp Ile Pro Lys Ile Ala Arg
 195 200 205
 Ser Phe Tyr Asp Leu Phe Glu Gln Lys Val Tyr His Arg Ser Leu Phe
 210 215 220
 Ile Glu Tyr Gly Lys Ala Leu Gly Ser Ser Thr Gly Ser Lys Ala
 225 230 235 240
 Glu Ser Leu Phe Val Asn Ile Phe Met Gln Ala Tyr Gly Ala Gly Gln
 245 250 255
 Thr Met Leu Arg Trp Gly Val Ile Ala Arg Ser Ser Asn Asn Ile Met
 260 265 270
 Leu Gly His Val Ser Val Gln Ala Glu Leu Lys Gln Val Thr Glu Val
 275 280 285
 Tyr Asp Leu Val Arg Glu Met Gly Pro Glu Ser Gly Leu Leu His Leu
 290 295 300
 Arg Gln Ser Pro Lys Ala Gly Leu Leu Ser Leu Ala Asn Cys Pro Asn
 305 310 315 320
 Phe Ala Ser Val Val Leu Gly Asn Ala Ser Gly Leu Gly Ile Ile Gly
 325 330 335
 Met Tyr Arg Gly Arg Val Pro Asn Thr Glu Leu Phe Ser Ala Ala Glu
 340 345 350
 Ser Tyr Ala Lys Ser Leu Lys Glu Ser Asn Lys Ile Asn Phe Ser Ser
 355 360 365
 Leu Gly Leu Thr Asp Glu Glu Lys Glu Ala Ala Glu His Phe Leu Asn
 370 375 380
 Val Ser Asp Asp Ser Gln Asn Asp Tyr Glu
 385 390

<210> 71

<211> 394

<212> PRT

<213> human Metapneumo virus

<400> 71

Met Ser Leu Gln Gly Ile His Leu Ser Asp Leu Ser Tyr Lys His Ala
 1 5 10 15
 Ile Leu Lys Glu Ser Gln Tyr Thr Ile Lys Arg Asp Val Gly Thr Thr
 20 25 30
 Thr Ala Val Thr Pro Ser Ser Leu Gln Gln Glu Ile Thr Leu Leu Cys
 35 40 45
 Gly Glu Ile Leu Tyr Ala Lys His Ala Asp Tyr Lys Tyr Ala Ala Glu
 50 55 60
 Ile Gly Ile Gln Tyr Ile Ser Thr Ala Leu Gly Ser Glu Arg Val Gln
 65 70 75 80
 Gln Ile Leu Arg Asn Ser Gly Ser Glu Val Gln Val Val Leu Thr Arg
 85 90 95
 Thr Tyr Ser Leu Gly Lys Val Lys Asn Asn Lys Gly Glu Asp Leu Gln
 100 105 110
 Met Leu Asp Ile His Gly Val Glu Lys Ser Trp Val Glu Glu Ile Asp
 115 120 125
 Lys Glu Ala Arg Lys Thr Met Ala Thr Leu Leu Lys Glu Ser Ser Gly
 130 135 140
 Asn Ile Pro Gln Asn Gln Arg Pro Ser Ala Pro Asp Thr Pro Ile Ile
 145 150 155 160
 Leu Leu Cys Val Gly Ala Leu Ile Phe Thr Lys Leu Ala Ser Thr Ile
 165 170 175
 Glu Val Gly Leu Glu Thr Thr Val Arg Arg Ala Asn Arg Val Leu Ser
 180 185 190
 Asp Ala Leu Lys Arg Tyr Pro Arg Met Asp Ile Pro Lys Ile Ala Arg
 195 200 205
 Ser Phe Tyr Asp Leu Phe Glu Gln Lys Val Tyr Tyr Arg Ser Leu Phe
 210 215 220
 Ile Glu Tyr Gly Lys Ala Leu Gly Ser Ser Thr Gly Ser Lys Ala
 225 230 235 240
 Glu Ser Leu Phe Val Asn Ile Phe Met Gln Ala Tyr Gly Ala Gly Gln
 245 250 255
 Thr Met Leu Arg Trp Gly Val Ile Ala Arg Ser Ser Asn Asn Ile Met
 260 265 270
 Leu Gly His Val Ser Val Gln Ala Glu Leu Lys Gln Val Thr Glu Val
 275 280 285
 Tyr Asp Leu Val Arg Glu Met Gly Pro Glu Ser Gly Leu Leu His Leu
 290 295 300
 Arg Gln Ser Pro Lys Ala Gly Leu Leu Ser Leu Ala Asn Cys Pro Asn
 305 310 315 320
 Phe Ala Ser Val Val Leu Gly Asn Ala Ser Gly Leu Gly Ile Ile Gly
 325 330 335
 Met Tyr Arg Gly Arg Val Pro Asn Thr Glu Leu Phe Ser Ala Ala Glu
 340 345 350
 Ser Tyr Ala Lys Ser Leu Lys Glu Ser Asn Lys Ile Asn Phe Ser Ser
 355 360 365
 Leu Gly Leu Thr Asp Glu Glu Lys Glu Ala Ala Glu His Phe Leu Asn
 370 375 380
 Val Ser Asp Asp Ser Gln Asn Asp Tyr Glu
 385 390

<210> 72
 <211> 394
 <212> PRT
 <213> human Metapneumo virus

<400> 72
 Met Ser Leu Gln Gly Ile His Leu Ser Asp Leu Ser Tyr Lys His Ala
 1 5 10 15
 Ile Leu Lys Glu Ser Gln Tyr Thr Ile Lys Arg Asp Val Gly Thr Thr
 20 25 30

Thr Ala Val Thr Pro Ser Ser Leu Gln Gln Glu Ile Thr Leu Leu Cys
 35 40 45
 Gly Glu Ile Leu Tyr Thr Lys His Thr Asp Tyr Lys Tyr Ala Ala Glu
 50 55 60
 Ile Gly Ile Gln Tyr Ile Cys Thr Ala Leu Gly Ser Glu Arg Val Gln
 65 70 75 80

 Gln Ile Leu Arg Asn Ser Gly Ser Glu Val Gln Val Val Leu Thr Lys
 85 90 95
 Thr Tyr Ser Leu Gly Lys Gly Lys Asn Ser Lys Gly Glu Leu Gln
 100 105 110
 Met Leu Asp Ile His Gly Val Glu Lys Ser Trp Ile Glu Glu Ile Asp
 115 120 125
 Lys Glu Ala Arg Lys Thr Met Val Thr Leu Leu Lys Glu Ser Ser Gly
 130 135 140
 Asn Ile Pro Gln Asn Gln Arg Pro Ser Ala Pro Asp Thr Pro Ile Ile
 145 150 155 160
 Leu Leu Cys Val Gly Ala Leu Ile Phe Thr Lys Leu Ala Ser Thr Ile
 165 170 175
 Glu Val Gly Leu Glu Thr Thr Val Arg Arg Ala Asn Arg Val Leu Ser
 180 185 190
 Asp Ala Leu Lys Arg Tyr Pro Arg Ile Asp Ile Pro Lys Ile Ala Arg
 195 200 205
 Ser Phe Tyr Glu Leu Phe Glu Gln Lys Val Tyr Tyr Arg Ser Leu Phe
 210 215 220
 Ile Glu Tyr Gly Lys Ala Leu Gly Ser Ser Thr Gly Ser Lys Ala
 225 230 235 240
 Glu Ser Leu Phe Val Asn Ile Phe Met Gln Ala Tyr Gly Ala Gly Gln
 245 250 255
 Thr Leu Leu Arg Trp Gly Val Ile Ala Arg Ser Ser Asn Asn Ile Met
 260 265 270
 Leu Gly His Val Ser Val Gln Ser Glu Leu Lys Gln Val Thr Glu Val
 275 280 285
 Tyr Asp Leu Val Arg Glu Met Gly Pro Glu Ser Gly Leu Leu His Leu
 290 295 300
 Arg Gln Ser Pro Lys Ala Gly Leu Leu Ser Leu Ala Asn Cys Pro Asn
 305 310 315 320
 Phe Ala Ser Val Val Leu Gly Asn Ala Ser Gly Leu Gly Ile Ile Gly
 325 330 335
 Met Tyr Arg Gly Arg Val Pro Asn Thr Glu Leu Phe Ser Ala Ala Glu
 340 345 350
 Ser Tyr Ala Arg Ser Leu Lys Glu Ser Asn Lys Ile Asn Phe Ser Ser
 355 360 365
 Leu Gly Leu Thr Asp Glu Glu Lys Glu Ala Ala Glu His Phe Leu Asn
 370 375 380
 Met Ser Gly Asp Asn Gln Asn Asp Tyr Glu
 385 390

<210> 73
 <211> 394
 <212> PRT
 <213> human Metapneumo virus

<400> 73
 Met Ser Leu Gln Gly Ile His Leu Ser Asp Leu Ser Tyr Lys His Ala
 1 5 10 15
 Ile Leu Lys Glu Ser Gln Tyr Thr Ile Lys Arg Asp Val Gly Thr Thr
 20 25 30
 Thr Ala Val Thr Pro Ser Ser Leu Gln Gln Glu Ile Thr Leu Leu Cys
 35 40 45
 Gly Glu Ile Leu Tyr Thr Lys His Thr Asp Tyr Lys Tyr Ala Ala Glu

50	55	60
Ile	Gly	Ile Gln Tyr Ile Cys Thr Ala Leu Gly Ser Glu Arg Val Gln
65	70	75 80
Gln	Ile	Leu Arg Asn Ser Gly Ser Glu Val Gln Val Val Leu Thr Lys
		85 90 95
Thr	Tyr	Ser Leu Gly Lys Gly Lys Asn Ser Lys Gly Glu Glu Leu Gln
		100 105 110
Met	Leu	Asp Ile His Gly Val Glu Lys Ser Trp Val Glu Glu Ile Asp
		115 120 125
Lys	Glu	Ala Arg Lys Thr Met Val Thr Leu Leu Lys Glu Ser Ser Gly
		130 135 140
Asn	Ile	Pro Gln Asn Gln Arg Pro Ser Ala Pro Asp Thr Pro Ile Ile
		145 150 155 160
Leu	Leu	Cys Val Gly Ala Leu Ile Phe Thr Lys Leu Ala Ser Thr Ile
		165 170 175
Glu	Val	Gly Leu Glu Thr Thr Val Arg Arg Ala Asn Arg Val Leu Ser
		180 185 190
Asp	Ala	Leu Lys Arg Tyr Pro Arg Val Asp Ile Pro Lys Ile Ala Arg
		195 200 205
Ser	Phe	Tyr Glu Leu Phe Glu Gln Lys Val Tyr Tyr Arg Ser Leu Phe
		210 215 220
Ile	Glu	Tyr Gly Lys Ala Leu Gly Ser Ser Thr Gly Ser Lys Ala
		225 230 235 240
Glu	Ser	Leu Phe Val Asn Ile Phe Met Gln Ala Tyr Gly Ala Gly Gln
		245 250 255
Thr	Met	Leu Arg Trp Gly Val Ile Ala Arg Ser Ser Asn Asn Ile Met
		260 265 270
Leu	Gly	His Val Ser Val Gln Ala Glu Leu Lys Gln Val Thr Glu Val
		275 280 285
Tyr	Asp	Leu Val Arg Glu Met Gly Pro Glu Ser Gly Leu Leu His Leu
		290 295 300
Arg	Gln	Ser Pro Lys Ala Gly Leu Leu Ser Leu Ala Asn Cys Pro Asn
		305 310 315 320
Phe	Ala	Ser Val Val Leu Gly Asn Ala Ser Gly Leu Gly Ile Ile Gly
		325 330 335
Met	Tyr	Arg Gly Arg Val Pro Asn Thr Glu Leu Phe Ser Ala Ala Glu
		340 345 350
Ser	Tyr	Ala Arg Ser Leu Lys Glu Ser Asn Lys Ile Asn Phe Ser Ser
		355 360 365
Leu	Gly	Leu Thr Asp Glu Glu Lys Glu Ala Ala Glu His Phe Leu Asn
		370 375 380
Met	Ser	Asp Asp Asn Gln Asp Asp Tyr Glu
		385 390

<210> 74
<211> 1185
<212> DNA
<213> human Metapneumo virus

<400> 74
atgtctcttc aaggattca cctgagtat ttatcataca agcatgtat attaaaagag 60
tctcagtaca caataaaaaag agatgtgggt acaaacaactg cagtgcaccc ctcatcattg 120
caacaagaaa taacactgtt gtgtggagaa attctgtatg ctaaacatgc tgactacaaa 180
tatgtctcgag aaataggaat acaaataatt agcacagctt taggatcaga gagagtgcag 240
cagattctga ggaactcagg cagtgaagtc caagtggctc taaccagaac gtactctctg 300
gggaaaatta aaaacaataa aggagaagat ttacagatgt tagacataca cggggtagag 360
aagagctgg tagaagagat agacaaagaa gcaaggaaaa caatggcaac ctggcttaag 420
gaatcatcag gtaatatccc acaaaatcag aggccctcag caccagacac acccataatc 480
ttattatgtg tagtgcctt aatattcaact aaactagcat caaccataga atgaaaacta 540
gagaccacag tcagaaggc taaccgtgta ctaagtatg cactcaagag ataccctaga 600
atggacatac caaagattgc cagatccttc tatgacttat ttgaacaaaa atgttatcac 660

agaagtttgt tcatttagta tggcaaagca ttaggctcat catctacagg cagcaaagca 720
 gaaagtctat ttgttaatat attcatgcaa gcttatgggg ccggtaaac aatgctaagg 780
 tgggggtca ttgcaggc atccaacaat ataatgttag gacatgtatc cgccaagct 840
 gagttaaaac aggtcacaga agtctatgac ttgtgcgag aaatggccc tgaatctgg 900
 cttctacatt taaggcaaag cccaaaagct ggactgttat cactagccaa ctgtcccaac 960
 tttgcaagtg ttgtctcgaa atatgcctca ggcttaggca taatcggtat gtatcgaggg 1020
 agagtaccaa acacagaatt atttcagca gctgaaagtt atgccaaaag tttgaaagaa 1080
 agcaataaaa taaatttc ttcatttagga cttacagatg aagagaaaga ggctgcagaa 1140
 catttcttaa atgtgagtgca cgacagtcaa aatgattatg agtaa 1185

<210> 75
 <211> 1185
 <212> DNA
 <213> human Metapneumo virus

<400> 75
 atgtctcttc aaggattca cctgagtat ctatcataca agcatgtat attaaaagag 60
 tctcagtata caataaaagag agatgttagc acaacaaccg cagtgacacc ctcatttt 120
 caacaagaaa taacactatt gtgtggagaa attctatatg ctaagcatgc tgattacaaa 180
 tatgtctcgag aaataggaat acaatatatt agcacagtc taggatcaga gagagtacag 240
 cagattctaa gaaactcagg tagtgaagtc caagtggttt taaccagaac gtactccttg 300
 gggaaaagttt aaaacaacaa aggagaagat ttacagatgt tagacatatac cggagtagag 360
 aaaagctggg tggaaagagat agacaaagaa gcaagaaaaaa caatggcaac tttgcttaaa 420
 gaatcatcag gcaatattcc acaaaaatcag aggccctcag caccagacac accataatc 480
 ttattatgtg taggtgcctt aatatttacc aaactagcat caactataga agtgggatta 540
 gagaccacag tcagaagagc taaccgtgtta ctaagtgtat cactaaaag ataccctagg 600
 atggacatac caaaaatcgc tagatcttc tatgacttat ttgaacaaaa agtgttattac 660
 agaagtttgt tcatttagta tggcaaagca ttaggctcat cctctacagg cagcaaagca 720
 gaaagtttat tcgttaatat attcatgcaa gcttacgggt ctggtaaac aatgctgagg 780
 tggggagtc ttcaggcattc atctaacaat ataatgttag gacatgtatc tttcaagct 840
 gagttaaaac aagtccacaga agtctatgac ctgtgcgag aaatggccc tgaatctggg 900
 ctccctacatt taaggcaaaag cccaaaagct ggactgttat cactagccaa ttgtcccaac 960
 tttgctagtg ttgtctcgaa caatgcctca ggcttaggca taataggtat gtatcgccgg 1020
 agagtgcacaa acacagaact atttcagca gcagaaagct atgccaagag tttgaaagaa 1080
 agcaataaaa ttaactttc ttcatttagga cttacagatg aagaaaaaga ggctgcagaa 1140
 cacttcttaa atgtgagtgca cgacagtcaa aatgattatg agtaa 1185

<210> 76
 <211> 1185
 <212> DNA
 <213> human Metapneumo virus

<400> 76
 atgtctcttc aaggattca cctaagtat ctatcataca aacatgtat attaaaagag 60
 tctcaataaca caataaaaag agatgttagc accacaactg cagtgacacc ttcattt 120
 caacaagaaa taacactttt gtgtgggaa atacttaca ctaaacacac tgattacaaa 180
 tatgtctcgag agataggaat acaatatatt tgcacagtc taggatcaga aagagtacaa 240
 cagatttga gaaactcagg tagtgaagtt cagtggttt taacaaaac atactcctt 300
 gggaaaaggca aaaacagtaa agggaaagag ctgcagatgt tagatataca tggagtgaa 360
 aagagttgga tagaagaaat agacaaagag gcaagaaaga caatggtaac tttgcttaag 420
 gaatcatcag gtaacatccc acaaaaaccg agacccctcag caccagacac accaataatt 480
 ttattatgtg taggtgcctt aatatttacc aaactagcat caacaataga agttggatta 540
 gagactacag tttagaagagc taatagagt ctaagtgtat cactaaaag ataccctagg 600
 atagatatac caaagattgc tagatcttt tatgaactat ttgaacaaaa agtgttactac 660
 agaagtttat tcatttagta cggaaaagct ttaggctcat cttcaacagg aagcaaagca 720
 gaaagtttgt ttgttaatat atttatgcaa gcttatggag ctggccaaac actgctaagg 780
 tgggggtc ttcaggcattc atccaacaat ataatgttag ggcattgtatc tttcaatct 840
 gaattgaagc aagtccacaga gttttagac ttgtgcgag aaatgggtcc tgaatctggg 900
 cttttacatc taagacaaag tccaaagca gggctgttat cattggccaa ttgtcccaat 960
 tttgctagtg ttgtctcgaa caatgcctca ggcttaggca taatcgaaat gtacagaggg 1020
 agagtaccaa acacagatg attttctgc gcaagaaagtt atgcccagaag cttaaaagaa 1080
 agcaataaaa tcaacttctc ttcgttaggg cttacagatg aagaaaaaga agctgcagaa 1140

cacttcttaa acatgagtgg tgacaatcaa aatgattatg agtaa

1185

<210> 77
<211> 1185
<212> DNA
<213> human Metapneumo virus

<400> 77
atgtcttc aaggattca cctaagtat ctgtcatata aacatgctat attaaaagag 60
tctcaataca caataaaaag agatgttaggc accacaactg cagtgcacacc ttcatcattg 120
cagcaagaga taacacttt gtgtggagag attctttaca ctaaacatac tgattacaaa 180
tatgctgcag agatagggat acaatatatt tgacacagctc taggatcaga aagagtacaa 240
cagattttaa gaaattcagg tagtgaggtt caggtggttc taaccaagac atactctta 300
gggaaaggta aaaatagtaa aggggaagag ttgcaaattgt tagatataca tggagtggaa 360
aagagttggg tagaagaaat agacaaagag gcaagaaaaa caatggtgac tttgctaaag 420
gaatcatcag gcaacatccc acaaaaccc aggccttcag caccagacacc accaataatt 480
ttattgtgtg taggtgcttt aatattcact aaactagcat caacaataga agttggacta 540
gagactacag tttagaagggc taacagagtg ttaagtgtat cgctcaaaag ataccctagg 600
tagatatac caaagattgc tagatcttt tatgaactat ttgagcagaa agtgttattac 660
aggagtctat tcattgagta tggaaaagct tttaggctcat cttcaacagg aagcaaaagca 720
gaaagtttgt ttgttaaatat atttatgcaa gcttatggag ccggtcagac aatgctaagg 780
tgggggtgtca ttgcagatc atctaacaac ataatgttag ggcatgtatc tggcaagct 840
gaattgaaac aagttacaga ggtttatgtat ttggttaagag aaatgggtcc tgaatctggg 900
cttttacatc taagacaaaag tccaaaggca ggactgttat cttggctaa ttgccccaaat 960
tttgcttagtg ttgttcttgg taatgctca ggtcttagta taatcggaat gtacagggga 1020
agagtgc当地 acacagagct atttctgca gcagaaaggt atgccagaag cttaaaaagaa 1080
agcaacaaaaa tcaacttctc ctcattaggg ctcacagacg aagaaaaaga agctgcagaa 1140
cacttcttaa acatgagtga tgacaatcaa gatgattatg agtaa 1185

<210> 78
<211> 294
<212> PRT
<213> human Metapneumo virus

<400> 78
Met Ser Phe Pro Glu Gly Lys Asp Ile Leu Phe Met Gly Asn Glu Ala
1 5 10 15
Ala Lys Leu Ala Glu Ala Phe Gln Lys Ser Leu Arg Lys Pro Gly His
20 25 30
Lys Arg Ser Gln Ser Ile Ile Gly Glu Lys Val Asn Thr Val Ser Glu
35 40 45
Thr Leu Glu Leu Pro Thr Ile Ser Arg Pro Ala Lys Pro Thr Ile Pro
50 55 60
Ser Glu Pro Lys Leu Ala Trp Thr Asp Lys Gly Gly Ala Thr Lys Thr
65 70 75 80
Glu Ile Lys Gln Ala Ile Lys Val Met Asp Pro Ile Glu Glu Glu
85 90 95
Ser Thr Glu Lys Lys Val Leu Pro Ser Ser Asp Gly Lys Thr Pro Ala
100 105 110
Glu Lys Lys Leu Lys Pro Ser Thr Asn Thr Lys Lys Val Ser Phe
115 120 125
Thr Pro Asn Glu Pro Gly Lys Tyr Thr Lys Leu Glu Lys Asp Ala Leu
130 135 140
Asp Leu Leu Ser Asp Asn Glu Glu Asp Ala Glu Ser Ser Ile Leu
145 150 155 160
Thr Phe Glu Glu Arg Asp Thr Ser Ser Leu Ser Ile Glu Ala Arg Leu
165 170 175
Glu Ser Ile Glu Glu Lys Leu Ser Met Ile Leu Gly Leu Leu Arg Thr
180 185 190
Leu Asn Ile Ala Thr Ala Gly Pro Thr Ala Ala Arg Asp Gly Ile Arg
195 200 205
Asp Ala Met Ile Gly Val Arg Glu Glu Leu Ile Ala Asp Ile Ile Lys

210	215	220
Glu Ala Lys Gly Lys Ala Ala Glu Met Met	Glu Glu Glu Met Ser Gln	
225	230	235
Arg Ser Lys Ile Gly Asn Gly Ser Val	Lys Leu Thr Glu Lys Ala Lys	240
245	250	255
Glu Leu Asn Lys Ile Val Glu Asp Glu Ser Thr Ser Gly	Glu Ser Glu	
260	265	270
Glu Glu Glu Pro Lys Asp Thr Gln Asp Asn Ser Gln	Glu Asp Asp	
275	280	285
Ile Tyr Gln Leu Ile Met		
290		

<210> 79
<211> 294
<212> PRT
<213> human Metapneumo virus

<400> 79		
Met Ser Phe Pro Glu Gly Lys Asp Ile Leu Phe Met Gly Asn Glu Ala		
1	5	10
Ala Lys Leu Ala Glu Ala Phe Gln Lys Ser Leu Arg Lys Pro Asn His		15
20	25	30
Lys Arg Ser Gln Ser Ile Ile Gly Glu Lys Val Asn Thr Val Ser Glu		
35	40	45
Thr Leu Glu Leu Pro Thr Ile Ser Arg Pro Thr Lys Pro Thr Ile Leu		
50	55	60
Ser Glu Pro Lys Leu Ala Trp Thr Asp Lys Gly Gly Ala Ile Lys Thr		
65	70	75
80		
Glu Ala Lys Gln Thr Ile Lys Val Met Asp Pro Ile Glu Glu Glu		
85	90	95
Phe Thr Glu Lys Arg Val Leu Pro Ser Ser Asp Gly Lys Thr Pro Ala		
100	105	110
Glu Lys Lys Leu Lys Pro Ser Thr Asn Thr Lys Lys Val Ser Phe		
115	120	125
Thr Pro Asn Glu Pro Gly Lys Tyr Thr Lys Leu Glu Lys Asp Ala Leu		
130	135	140
Asp Leu Leu Ser Asp Asn Glu Glu Asp Ala Glu Ser Ser Ile Leu		
145	150	155
160		
Thr Phe Glu Glu Arg Asp Thr Ser Ser Leu Ser Ile Glu Ala Arg Leu		
165	170	175
Glu Ser Ile Glu Lys Leu Ser Met Ile Leu Gly Leu Leu Arg Thr		
180	185	190
Leu Asn Ile Ala Thr Ala Gly Pro Thr Ala Ala Arg Asp Gly Ile Arg		
195	200	205
Asp Ala Met Ile Gly Ile Arg Glu Glu Leu Ile Ala Asp Ile Ile Lys		
210	215	220
Glu Ala Lys Gly Lys Ala Ala Glu Met Met Glu Glu Glu Met Asn Gln		
225	230	235
240		
Arg Thr Lys Ile Gly Asn Gly Ser Val Lys Leu Thr Glu Lys Ala Lys		
245	250	255
Glu Leu Asn Lys Ile Val Glu Asp Glu Ser Thr Ser Gly Glu Ser Glu		
260	265	270
Glu Glu Glu Pro Lys Asp Thr Gln Glu Asn Asn Gln Glu Asp Asp		
275	280	285
Ile Tyr Gln Leu Ile Met		
290		

<210> 80
<211> 294
<212> PRT

<213> human Metapneumo virus

<400> 80

Met Ser Phe Pro Glu Gly Lys Asp Ile Leu Phe Met Gly Asn Glu Ala
 1 5 10 15
 Ala Lys Ile Ala Glu Ala Phe Gln Lys Ser Leu Lys Lys Ser Gly His
 20 25 30
 Lys Arg Thr Gln Ser Ile Val Gly Glu Lys Val Asn Thr Ile Ser Glu
 35 40 45
 Thr Leu Glu Leu Pro Thr Ile Ser Lys Pro Ala Arg Ser Ser Thr Leu
 50 55 60
 Leu Glu Pro Lys Leu Ala Trp Ala Asp Asn Ser Gly Ile Thr Lys Ile
 65 70 75 80
 Thr Glu Lys Pro Ala Thr Lys Thr Asp Pro Val Glu Glu Glu
 85 90 95
 Phe Asn Glu Lys Lys Val Leu Pro Ser Ser Asp Gly Lys Thr Pro Ala
 100 105 110
 Glu Lys Lys Ser Lys Phe Ser Thr Ser Val Lys Lys Val Ser Phe
 115 120 125
 Thr Ser Asn Glu Pro Gly Lys Tyr Thr Lys Leu Glu Lys Asp Ala Leu
 130 135 140
 Asp Leu Leu Ser Asp Asn Glu Glu Asp Ala Glu Ser Ser Ile Leu
 145 150 155 160
 Thr Phe Glu Glu Lys Asp Thr Ser Ser Leu Ser Ile Glu Ala Arg Leu
 165 170 175
 Glu Ser Ile Glu Lys Leu Ser Met Ile Leu Gly Leu Leu Arg Thr
 180 185 190
 Leu Asn Ile Ala Thr Ala Gly Pro Thr Ala Ala Arg Asp Gly Ile Arg
 195 200 205
 Asp Ala Met Ile Gly Ile Arg Glu Glu Leu Ile Ala Glu Ile Ile Lys
 210 215 220
 Glu Ala Lys Gly Lys Ala Ala Glu Met Met Glu Glu Glu Met Asn Gln
 225 230 235 240
 Arg Ser Lys Ile Gly Asn Gly Ser Val Lys Leu Thr Glu Lys Ala Lys
 245 250 255
 Glu Leu Asn Lys Ile Val Glu Asp Glu Ser Thr Ser Gly Glu Ser Glu
 260 265 270
 Glu Glu Glu Glu Pro Lys Glu Thr Gln Asp Asn Asn Gln Gly Glu Asp
 275 280 285
 Ile Tyr Gln Leu Ile Met
 290

<210> 81

<211> 294

<212> PRT

<213> human Metapneumo virus

<400> 81

Met Ser Phe Pro Glu Gly Lys Asp Ile Leu Phe Met Gly Asn Glu Ala
 1 5 10 15
 Ala Lys Ile Ala Glu Ala Phe Gln Lys Ser Leu Lys Arg Ser Gly His
 20 25 30
 Lys Arg Thr Gln Ser Ile Val Gly Glu Lys Val Asn Thr Ile Ser Glu
 35 40 45
 Thr Leu Glu Leu Pro Thr Ile Ser Lys Pro Ala Arg Ser Ser Thr Leu
 50 55 60
 Leu Glu Pro Lys Leu Ala Trp Ala Asp Ser Ser Gly Ala Thr Lys Thr
 65 70 75 80
 Thr Glu Lys Gln Thr Lys Thr Asp Pro Val Glu Glu Glu
 85 90 95
 Leu Asn Glu Lys Lys Val Ser Pro Ser Asp Gly Lys Thr Pro Ala

100	105	110
Glu Lys Lys Ser Lys Ser Pro Thr Asn Val Lys Lys Val Ser Phe		
115	120	125
Thr Ser Asn Glu Pro Gly Lys Tyr Thr Lys Leu Glu Lys Asp Ala Leu		
130	135	140
Asp Leu Leu Ser Asp Asn Glu Glu Asp Ala Glu Ser Ser Ile Leu		
145	150	155
Thr Phe Glu Glu Arg Asp Thr Ser Ser Leu Ser Ile Glu Ala Arg Leu		
165	170	175
Glu Ser Ile Glu Lys Leu Ser Met Ile Leu Gly Leu Leu Arg Thr		
180	185	190
Leu Asn Ile Ala Thr Ala Gly Pro Thr Ala Ala Arg Asp Gly Ile Arg		
195	200	205
Asp Ala Met Ile Gly Ile Arg Glu Glu Leu Ile Ala Glu Ile Ile Lys		
210	215	220
Glu Ala Lys Gly Lys Ala Ala Glu Met Met Glu Glu Met Asn Gln		
225	230	235
Arg Ser Lys Ile Gly Asn Gly Ser Val Lys Leu Thr Glu Lys Ala Lys		
245	250	255
Glu Leu Asn Lys Ile Val Glu Asp Glu Ser Thr Ser Gly Glu Ser Glu		
260	265	270
Glu Glu Glu Pro Lys Glu Thr Gln Asp Asn Asn Gln Gly Glu Asp		
275	280	285
Ile Tyr Gln Leu Ile Met		
290		

<210> 82
<211> 885
<212> DNA
<213> human Metapneumo virus

<400> 82
atgtcattcc ctgaaggaaa agatattctt ttcatggta atgaagcagc aaaattagca 60
gaagctttcc agaaatcatt aagaaaaacca ggtcataaaa gatctcaatc tattatagga 120
gaaaaaagtga atactgtatc agaaacattg gaattaccta ctatcagtag acctgc当地 180
ccaaccatac cgtcagaacc aaagttagca tggacagata aaggtgggc aacccaaaact 240
gaaataaaagc aagaatcaa agtcatggat cccattgaag aagaagagtc taccgagaag 300
aaggtgctac cctccagtga tggaaaaacc cctgcagaaaa agaaactgaa accatcaact 360
aacacaaaaa agaaggttc atttacacca aatgaaccag ggaaatatac aaagttggaa 420
aaagatgctc tagatttgct ctcagataat gaagaagaag atgcagaatc ttcaatctt 480
acctttgaag aaagagatac ttcatcatta agcattgagg ccagattgga atcaatagag 540
gagaaattaa gcatgatatt aggcttata agaacactca acattgctac agcaggacc 600
acagcagcaa gagatggat cagagatgca atgattggcg taagagagga attaatagca 660
gacataataa aggaagctaa agggaaaagca gcagaaatga tggaaagagga aatgagtcaa 720
cgatcaaaaa taggaaatgg tagtgtaaaa ttaacagaaaa aagcaaaaaga gctcaacaaa 780
attgttgaag atgaaagcac aagtggagaa tccgaagaag aagaagaacc aaaagacaca 840
caagacaata gtcaagaaga tgacatttac cagttatta tgtag 885

<210> 83
<211> 885
<212> DNA
<213> human Metapneumo virus

<400> 83
atgtcattcc ctgaaggaaa agatattctt ttcatggta atgaagcagc aaaattggca 60
gaagctttcc aaaaatcatt aagaaaaacct aatcataaaa gatctcaatc tattatagga 120
gaaaaaagtga acactgtatc tggaaacattg gaattaccta ctatcagtag acctaccaaa 180
ccgaccatat tgtcagagcc gaagttagca tggacagaca aaggtgggc aatccaaaact 240
gaagcaaaagc aaacaatcaa agttatggat cctattgaag aagaagagtt tactgagaaa 300
agggtgctgc cctccagtga tggaaaaact cctgcagaaaa agaagtgaa accatcaacc 360
aacactaaaa agaaggcttc atttacacca aatgaaccag gaaaatcacac aaagttggag 420

aaagatgctc tagacttgct ttcagacaat gaagaagaag atgcagaatc ctcaatctta 480
 accttcgaag aaagagatac ttcatcatta agcattgaag ccagactaga atcgatttag 540
 gagaaattaa gcatgatatt agggctatta agaacactca acattgctac agcaggaccc 600
 acagcagcaa gagatggat cagagatgca atgattggca taagggagga actaatagca 660
 gacataataa aagaagccaa gggaaaagca gcagaaaatga tggagaaga aatgaaccag 720
 cggacaaaaa taggaaacgg tagtgtaaaa ttaactgaaa aggcaaagga gctcaacaaa 780
 attgttgaag acgaaagcac aagtggtaa tccgaagaag aagaagaacc aaaagacaca 840
 caggaaaata atcaagaaga tgacatttac cagttatca tgttag 885

<210> 84

<211> 885

<212> DNA

<213> human Metapneumo virus

<400> 84

atgtcattcc ctgaaggaaa ggatattctg ttcatggta atgaagcagc aaaaatagcc 60
 gaagcttcc agaaatcact gaaaaatca ggtcacaaga gaactcaatc tattgttaggg 120
 gaaaaagttt acacttatc agaaactcta gaactaccta ccatcagcaa acctgcacga 180
 tcacatctacac tgcttggacc aaaattggca tggcagaca acagcgaat caccaaaatc 240
 acagaaaaac cagaacacca aacaacagat cctgttgaag aagaggaatt caatgaaaag 300
 aaagtgttac cttccagtga tggaaagact cctgcagaga aaaaatcaaa gtttcaacc 360
 agtgtaaaaa agaaagttc ctttacatca aatgaaccag gaaaatacac caaactagag 420
 aaagatgccccc tagatttgc ttcagacaat gagaagaag acgcagaatc ctcaatccta 480
 acttttgagg agaaagatac atcatacta agcattgaag cttagactaga atctatagaa 540
 gagaagttga gcatgatatt aggactgctt cgtacactta acattgcaac agcaggacca 600
 acagctgac gagatggat tagggatgca atgattggta taagagaaga gctaatacg 660
 gagataatta aggaagccaa gggaaaagca gctgaaatga tggagaaga gatgaatcaa 720
 agatcaaaaa taggaaatgg cagttaaaa ctaaccgaga aggcaaaaga gctcaacaaa 780
 attgttgaag acgagagcac aagcggtgaa tcagaagaag aagaagaacc aaaagaaact 840
 caggataaca atcaaggaga agatatttac cagttatca tgttag 885

<210> 85

<211> 885

<212> DNA

<213> human Metapneumo virus

<400> 85

atgtcattcc ctgaaggaaa agatattcctg ttcatggta atgaagcagc aaaaatagca 60
 gaagcttcc agaaatcact aaaaagatca ggtcacaaaa gaacctcagtc tattgttaggg 120
 gaaaaagttt acacttatc agaaactcta gagctaccta ccatcagcaa acctgcacga 180
 tcacatctacac tgcttagagcc aaaattggca tggcagaca gcagcggagc caccaaaacc 240
 acagaaaaac aaacaacca aacaacagat cctgttgaag aagaggaact caatgaaaag 300
 aaggtatcac cttccagtga tggaaagact cctgcagaga aaaaatcaaa atctccaacc 360
 aatgtaaaaa agaaagttc cttcacatca aatgaaccag gaaaatatac taaaactagaa 420
 aaagatgccccc tagatttgc ttcagacaat gagaagaag acgcagagtc ctcaatccta 480
 acctttgaag agagagacac atcatacta agcattgagg cttagactaga atcaatacg 540
 gagaagctaa gcatgatatt aggactgctt cgtacactta acattgcaac agcaggacca 600
 acggctgcaaa gggatggat cagagatgca atgattggta taagagaaga actaatagca 660
 gaaataataa aagaagccaa gggaaaagca gcccataatga tggaaagagga aatgaatcaa 720
 aggtcaaaaa taggaaatgg cagttaaaa ctaaccgaga aggcaaaaga acttaataaa 780
 attgttgaag acgagagcac aagtggtgaa tcagaagaag aagaagaacc aaaagaaact 840
 caggataaca atcaaggaga agatatctac cagttatca tgttag 885

<210> 86

<211> 183

<212> PRT

<213> human Metapneumo virus

<400> 86

Met Ile Thr Leu Asp Val Ile Lys Ser Asp Gly Ser Ser Lys Thr Cys
 1 5 10 15
 Thr His Leu Lys Ile Ile Lys Asp His Ser Gly Lys Val Leu Ile

20	25	30
Val Leu Lys Leu Ile Leu Ala Leu Leu Thr Phe Leu Thr Val Thr Ile		
35	40	45
Thr Ile Asn Tyr Ile Lys Val Glu Asn Asn Leu Gln Ile Cys Gln Ser		
50	55	60
Lys Thr Glu Ser Asp Lys Lys Asp Ser Ser Ser Asn Thr Thr Ser Val		
65	70	75
80		
Thr Thr Lys Thr Thr Leu Asn His Asp Ile Thr Gln Tyr Phe Lys Ser		
85	90	95
Leu Ile Gln Arg Tyr Thr Asn Ser Ala Ile Asn Ser Asp Thr Cys Trp		
100	105	110
Lys Ile Asn Arg Asn Gln Cys Thr Asn Ile Thr Thr Tyr Lys Phe Leu		
115	120	125
Cys Phe Lys Ser Glu Asp Thr Lys Thr Asn Asn Cys Asp Lys Leu Thr		
130	135	140
Asp Leu Cys Arg Asn Lys Pro Lys Pro Ala Val Gly Val Tyr His Ile		
145	150	155
160		
Val Glu Cys His Cys Ile Tyr Thr Val Lys Trp Lys Cys Tyr His Tyr		
165	170	175
Pro Thr Asp Glu Thr Gln Ser		
180		

<210> 87

<211> 179

<212> PRT

<213> human Metapneumo virus

<400> 87

Met Ile Thr Leu Asp Val Ile Lys Ser Asp Gly Ser Ser Lys Thr Cys		
1	5	10
15		
Thr His Leu Lys Lys Ile Ile Lys Asp His Ser Gly Lys Val Leu Ile		
20	25	30
Ala Leu Lys Leu Ile Leu Ala Leu Leu Thr Phe Phe Thr Ile Thr Ile		
35	40	45
Thr Ile Asn Tyr Ile Lys Val Glu Asn Asn Leu Gln Ile Cys Gln Ser		
50	55	60
Lys Thr Glu Ser Asp Lys Glu Asp Ser Pro Ser Asn Thr Thr Ser Val		
65	70	75
80		
Thr Thr Lys Thr Thr Leu Asp His Asp Ile Thr Gln Tyr Phe Lys Arg		
85	90	95
Leu Ile Gln Arg Tyr Thr Asp Ser Val Ile Asn Lys Asp Thr Cys Trp		
100	105	110
115	120	125
Lys Ile Ser Arg Asn Gln Cys Thr Asn Ile Thr Thr Tyr Lys Phe Leu		
Cys Phe Lys Pro Glu Asp Ser Lys Ile Asn Ser Cys Asp Arg Leu Thr		
130	135	140
Asp Leu Cys Arg Asn Lys Ser Lys Ser Ala Ala Glu Ala Tyr His Thr		
145	150	155
160		
Val Glu Cys His Cys Ile Tyr Thr Ile Glu Trp Lys Cys Tyr His His		
165	170	175
Pro Ile Asp		

<210> 88

<211> 177

<212> PRT

<213> human Metapneumo virus

<400> 88

Met Lys Thr Leu Asp Val Ile Lys Ser Asp Gly Ser Ser Glu Thr Cys

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			20			25						30			
Ala	Leu	Lys	Leu	Ile	Leu	Ala	Leu	Leu	Thr	Phe	Phe	Thr	Ala	Thr	Ile
			35			40						45			
Thr	Val	Asn	Tyr	Ile	Lys	Val	Glu	Asn	Asn	Leu	Gln	Ala	Cys	Gln	Pro
			50			55					60				
Lys	Asn	Glu	Ser	Asp	Lys	Val	Thr	Lys	Pro	Asn	Thr	Thr	Ser	Thr	
			65			70					75			80	
Thr	Ile	Arg	Pro	Thr	Pro	Asp	Pro	Thr	Val	Val	His	His	Leu	Lys	Arg
			85			90					95				
Leu	Ile	Gln	Arg	His	Thr	Asn	Ser	Val	Thr	Lys	Asp	Ser	Asp	Thr	Cys
			100			105					110				
Trp	Arg	Ile	His	Lys	Asn	Gln	Arg	Thr	Asn	Ile	Lys	Ile	Tyr	Lys	Phe
			115			120					125				
Leu	Cys	Ser	Gly	Phe	Thr	Asn	Ser	Lys	Gly	Thr	Asp	Cys	Glu	Glu	Pro
			130			135					140				
Thr	Ala	Leu	Cys	Asp	Lys	Lys	Leu	Lys	Thr	Ile	Val	Glu	Lys	His	Arg
			145			150					155			160	
Lys	Ala	Glu	Cys	His	Cys	Leu	His	Thr	Thr	Glu	Trp	Gly	Cys	Leu	His
			165			170					175				
pro															

<210> 89
<211> 177
<212> PRT
<213> human Metapneumo virus

1	5	10	15												
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Asn	Gln	Leu	Lys	Ile	Ile	Lys	Lys	His	Ser	Gly	Lys	Leu	Ile		
			35			40						45			
Ala	Leu	Lys	Leu	Ile	Leu	Ala	Leu	Leu	Thr	Phe	Phe	Thr	Val	Thr	Ile
			50			55					60				
Thr	Val	Asn	Tyr	Ile	Lys	Val	Glu	Asn	Asn	Leu	Gln	Ala	Cys	Gln	Leu
			65			70					75			80	
Lys	Asn	Glu	Ser	Asp	Lys	Asp	Thr	Lys	Leu	Asn	Thr	Thr	Ser	Thr	
			85			90					95				
Leu	Ile	Gln	Lys	His	Thr	Asn	Phe	Val	Ile	Lys	Asp	Arg	Asp	Thr	Cys
			100			105					110				
Trp	Arg	Ile	His	Thr	Asn	Gln	Cys	Thr	Asn	Ile	Lys	Ile	Tyr	Lys	Phe
			115			120					125				
Leu	Cys	Phe	Gly	Phe	Met	Asn	Ser	Thr	Asn	Thr	Asp	Cys	Glu	Glu	Leu
			130			135					140				
Thr	Val	Leu	Cys	Asp	Lys	Lys	Ser	Lys	Thr	Met	Thr	Glu	Lys	His	Arg
			145			150					155			160	
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Leu															

<210> 90
<211> 552
<212> DNA
<213> human Metapneumo virus

<400> 90

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<210> 91

<211> 540

<212> DNA

<213> human Metapneumo virus

<400> 91

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<210> 92

<211> 534

<212> DNA

<213> human Metapneumo virus

<400> 92

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<210> 93

<211> 534

<212> DNA

<213> human Metapneumo virus

<400> 93

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<210> 94
 <211> 13294
 <212> DNA
 <213> human metapneumo virus

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 <400> 94

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<211> 907

<212> DNA

<213> Human metapneumo virus

<400> 98

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<212> DNA
<213> Human metapneumo virus

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<212> DNA
<213> Human metapneumo virus

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ttgagtagtgc ccctaataat ctatctgatc ataaactata caatgcaga aaacacatcc 180
gaatcagaac atcacaccag ctcataccccc atgaatcca gcagggaaac tccaacggtc 240
cccatacgaca actcagacac caatccaggc tcacagtatc caactcaaca gtccacagaa 300
gactccacac tccactctgc agtccagca agtcaccag agacagaacc aacatcaaca 360
ccagacacaa caagccgccc gcccctcgac gacacacaca caacaccacc aagtgcagc 420
aggacaagga caagtccggc agtccacaca aaaaacaacc caaggtaag ccccagaacaa 480
cattccccac catggcaat gacaaggacg gtccgcccggaa ccaccactct ccgcacaagc 540
agcacaagaa aaagactgtc tacagcatca gtccaaacccg acagcagcgc aacaacccac 600

aaacacgaag aaacaagccc agtgagccca caaacatctg caagcacagc aagaccacaa 660
 aggaaggcca tggaggccag cacatcaaca acatacaacc aaactagttt aaaaaaaaata 720
 caaaaataact ctaagataaa ccatgttagac accaacaatt gagaagccaa aaggcaattc 780
 acaatctccc aaaaaaggca caacaccata ttagctccgc ttaaatctcc ctgaaaaaaaa 840
 cactcaccctata tataccaaact ataccacaac catccccaga aaaaaggctg ggcaaaacaa 900
 caccctaa 907

<210> 104
 <211> 908
 <212> DNA
 <213> Human metapneumo virus

<400> 104
 atggaggtga aagtggagaa cattcgaaca atagatatgc tcaaagcaag agtggaaaat 60
 cgtgtggcac gcagcaaatg cttaaaaaat gcctcttga tcctaataagg aataactaca 120
 tttagtatag ccctcaatat ctatctgatc ataaactata caatgcaga aacacatcc 180
 gaatcagaac atcacaccag ttcatcaccc atggaatcca gcaggaaac tccaaacggtc 240
 cctatggaca actcagacac caatccaggc tcacagtatc caactcaaca gtcccacagaa 300
 ggctccacac tccactttgc agcctcgca agtcaccagg agacagaacc aacatcaaca 360
 ccagacacaa caagccgccc gcccctcgca gacacacaca caacaccatc aagtgcgaagc 420
 agaacaaga caagtccgac agtccacaca aaaaacaatc taaggataag ccccgagaaca 480
 cattcccccac catggcaat gacaaggacg gtccgtggaa ccaccactt cccgcacaagc 540
 agcataagaa aaagaccgtc cacagcatca gtccaaacctg acagcagcgc aacaacccac 600
 aaacacgaag aagaagccc agtgagcccg caagcatctg caagcacagc aagaccacaa 660
 aggaaggcca tggaggccag cacaatcaaca acatacaacc aaactagttt aaaaaaaaata 720
 taaaataact ctaagataaa ccatgttagac accaacaattt gagaagccaa aaggcaattc 780
 acaatctccc aaaaaaggca acaacaccat attagctccg ttaaatctc cctggaaaaaa 840
 acactcgccc atataccaaac tataccacaa ccataccaaag gaaaaaagct gggtaaaaca 900
 acaccctaa 908

<210> 105
 <211> 908
 <212> DNA
 <213> Human metapneumo virus

<400> 105
 atggaggtga aagtggagaa cattcgaaca atagatatgc tcaaagcaag agtggaaaat 60
 cgtgtggcac gcagcaaatg cttaaaaaat gcctcttga tcctaataagg aataactaca 120
 tttagtatag ccctcaatat ctatctgatc ataaactata caatgcaga aacacatcc 180
 gaatcagaac atcacaccag ctcatcaccc atggaatcca gcaggaaac tccaaacggtc 240
 cctatggaca actcagacac caatccaggc tcacagtatc caactcaaca gtcccacagaa 300
 ggctccacac tccactttgc agcctcgca agtcaccagg agacagaacc aacatcaaca 360
 ccagacacaa caagccgccc gcccctcgca gacacacaca caacaccatc aagtgcgaagc 420
 agaataagaa caagtccgac agtccacaca aaaaacaatc taaggataag ccccgagaaca 480
 cattcccccac catggcaat gacaaggacg gtccgtggaa ccaccactt cccgcacaagc 540
 agcataagaa aaagaccgtc cacagcatca gtccaaacctg acagcagcgc aacaacccac 600
 aaacacgaag aagaagccc agtgagcccg caagcatctg caagcacagc aagaccacaa 660
 aggaaggcca tggaggccag cacaatcaaca acatacaacc aaactagttt aaaaaaaaata 720
 tacaataact ctaagataaa ccatgttagac accaacaattt gagaagccaa aaggcaattc 780
 acaatctccc aaaaaaggca acaacaccat attagctccg ttaagtctc cctggaaaaaa 840
 acactcgccc atataccaaac tataccacaa ccataccaaag gaaaaaagct gggcaaaaca 900
 acaccctaa 908

<210> 106
 <211> 888
 <212> DNA
 <213> Human metapneumo virus

<400> 106
 atggaggtga aagttagagaa cattcgagca atagacatgc tcaaagcaag agtggaaaat 60
 cgtgtggcac gtagcaaatg cttaaaaaat gcttctttaa tcctcatagg aataactaca 120
 ctgagttatag ctctcaatat ctatctgatc ataaactaca caataaaaaa aaccacatcc 180

gaatcagaac accacaccag ctcaccaccc acagaaccca acaaggaagc ttcaacaatc 240
 tccacagaca acccagacat caatccaagc tcacagcatc caactcaaca gtccacagaa 300
 aaccccacac tcaacccccgc agcatcaagc agcccatcg aaacagaacc agcatcaaca 360
 ccagacacaa caaacccgct gtccctccgt a gacagg tcca cagcacaacc aagt gaaagc 420
 agaacaaga caaaaaccgac agtccacaca atcaacaacc caaacacagc ttccagtaca 480
 caatccccac cacggacaac aacgaaggca atccgcagag ccaccactt cccgcatgagc 540
 agcacaggaa aaagaccaac cacaacatta gtccagtcg acagcagcac cacaacccaa 600
 aatcatgaag aaacaggttc agcgaaccca cagcgctctg caagcacaat gaaaaactag 660
 cacaccaata atataaaacc aaatttagtt aaaaaaaatg cgagatagct ctaaagcaaa 720
 acatgttagt accaacaatc aagaaaccaa aagacaactc acaatctccc taaaacagca 780
 acgacaccat gtcagcttg ctcaaatctc tctgggagaa acttctaccc acatactaac 840
 aacatcaca a ccatctcaag aaaagaaact gggcaaaaca gcatccaa 888

<210> 107

<211> 888

<212> DNA

<213> Human metapneumo virus

<400> 107

atggagggtga aagttagagaa cattcgagca atagacatgc tcaaagcaag agt gaaaaat 60
 cgtgtggcac gcagcaatg cttaaaaat gcttctttaa tcctcatagg aataactaca 120
 ctgagtata g cctcaatat ctatctgatc ataaactaca caataca aaaa aaccacatc 180
 gaatcagaac accacactag ctcaccaccc acagaatcca acaaagaac ttcaacaatc 240
 cccatagaca acccagacat caatccaaac tcacagcatc caacccaca g tccacagaa 300
 agccccacac tcaaccccg c agcctcggt agcccatcg aaacagaacc agcatcaaca 360
 ccagacacaa caaaccgc t gtcctccgt a gacagatcca caacacaacc aagt gaaagc 420
 agaacaaga caaaaaccac agtccacaca aaaaacaatc caagtacagt ttccagaaca 480
 caatccccac tacggcaac aacgaaggcg gtccctcagag ccaccgctt cccgacgagc 540
 agcacaagaa aaagaccaac cacaacatca gtcagtcg acagcagcac cacaacccaa 600
 aatcatgaag aaacaagttc agcgaaccca caggcatctg caagcacaat gcaaaagccag 660
 cacaccaaca acataaaacc aaatttagtt aaaaaaaata cgagatagct ctaaagtaaa 720
 acatgttagt accaacaatc aaggaatcaa aagacaactc acaatctccc taaaacagca 780
 acaacatcat gtcagtttg ctcaaatctc cctgggagaa acttctgccc acatactaac 840
 aacatcaca a ccatctcaag aaaagaaact gggcaaaaca gca cccaa 888

<210> 108

<211> 888

<212> DNA

<213> Human metapneumo virus

<400> 108

atggagggtga aagttagagaa catccgagca gtagacatgc tcaaagcaag agtcaaaaat 60
 cgtgtggcac gcagcaatg cttaaaaat gcctccttaa tcctcgtagg aataactaca 120
 ctgagcatag cctcaatat ctatctgatc gtaaactaca caataca aaaa aaccacatc 180
 gaatcagaac accacaccag ctcatcaccc acagaatcca acaaaggAAC ttcaacaatc 240
 cccacagaca acccagacat caatccaaat tcacaacatc caactcaaca g tccacagaa 300
 agccccacac tcaacaccgc agcctcggt agcccatcg aaacagaacc agcatcaaca 360
 ccagacacaa caaaccgc t gtcctccgc a gacagatcca caacacaacc aagt gaaagc 420
 agaacaaga caaagctgac agtccacaca aaaaacaacc taagtacagc ttccagaaca 480
 caatcaccac cacggcaac aacgaaggcg gtccctcagag acaccgctt ccacacgagc 540
 agcacaggaa aaagaccaac cacaacatca gtcagtcg acagcagcac cacaactcaa 600
 aatcatgaag aaacaagttc atcgaaccca caggcatctg caagcacaat gcaagaccag 660
 gacaccaaca atacaaaaca aaatttagtt aaaaaaaata caagatagct ctaaagtaaa 720
 acatgttagt accaacagta aagaaatcaa aagacaactc acaatctccc caaaacagca 780
 acaacatcat gtcagcttcg ctcaaatctc cctgggagaa actctcgccc acatactaac 840
 aacatcaca a ccatctcaag aaaagaaact gggcaaaaaaa acactcaa 888

<210> 109

<211> 887

<212> DNA

<213> Human metapneumo virus

<400> 109

atggaggtga aagttagagaa catccgagca gtagacatgc tcaaaggcaag agttaaaaat 60
 cgtgtggcac gcagcaaattt cttaaaaaat gcctctttaa tcctcgtagg aataactaca 120
 ctgagtagatcc ccctcaatat ctatctgatc gttaactaca caataaaaaa aaccacatcc 180
 gaatcagaac accacactag ctcaccc acagaatcca acaaaggaaac ttcaacaatc 240
 ccacagacaa cccagacatc aatccaaattt cacaacatcc aactcaacag tccacagaaa 300
 gcccccacact caacaccgca gcctcggtga gcccattcaga aacagaacca gcatcaacac 360
 cagacacaac aaaccgcctg tcctccgcag acagatccac aacacaacca agtggaaagca 420
 gaacaaagac aaagctgaca gtccacacaa aaaacaacctt aagtacagcc tccagaacac 480
 aatcaccacc acggcaaca acgaaggcggtt tcctcagaga caccgccttc cacacgagca 540
 gcacaggaaa aagaccaacc acaacatcag tccagtcgg cagcagcacc acaactcaaa 600
 atcatgaaga aacaagttca tcgaacccac aggcatctgc aagcacaatg caagaccagg 660
 acaccaacaa tacaaaacaa aattagttt caaaaaatac aagatagctc taaagtaaaa 720
 catgttaggtt ccaacagttt agaaatccaa agacaactca taatctcccc aaaacagcaa 780
 caacatcatg tcagcttcgc tcaaattcctc ctgggagaaa ctctcgccc catactaaca 840
 acatcacaac tatctcaaga aaagaaaactg ggcaaaaaaaaaa cactcaa 887

<210> 110

<211> 888

<212> DNA

<213> Human metapneumo virus

<400> 110

atggaggtga aagttagagaa cattcgagca atagacatgc tcaaaggcaag aatgaaaaat 60
 cgtgtggcac gcagcaaattt cttaaaaaat gcttcattaa tcctcgtagg aataactact 120
 ctgagtagatcc ccctcaatat ctatctgatc ataaactaca caataaaaaa aaccacatct 180
 gaatcagaac accacactag ctcaccc acagaatcca acaaaggaaac ttcaacaatc 240
 cctatagaca acccagacat caatccaaac tcacagcatc caactcaaca gtccacagaa 300
 agcctcacac tcaacccgc agcctcggtg agcccatcag aaacagaacc agcatcaaca 360
 ccagacacaa caaacccgcgtt tcctccgtt gacagatcca caacacaacc aagtggaaagc 420
 agaacaaaga aaaaactgac agtccacaaa aaaaacatcc caagtacagt ctctagaaca 480
 caatccctaa tacggcaac aacgaaggcg gtccctcagag ccaccgcctt tcgcacgagc 540
 agcacaggag aaagaccaac tacaaacatca gtccagtcgt acagcagcac cacaacccaa 600
 aatcatgaag aaacaggttc agcgaacccca caggcatctg caagcacaat gcaaaacttag 660
 cacaccaaca ttgtaaaacc aaattagttt aaaaaataa tgaaatagct ctaaagtaaaa 720
 acatgttaggtt gctaacaatc aagaaatccaa aagacatctc ataatctctc caaaacagca 780
 acaacatcatg tcacactttt ctcacatctc cctgggagaaa actttcgccc ccataactgac 840
 aacatcacaac tcacatctcaag aaaagaaaactt gggcaaaaca gcaccaaaa 888

<210> 111

<211> 888

<212> DNA

<213> Human metapneumo virus

<400> 111

atggaggtga aagttagagaa cattcgagca atagacatgc tcaaaggcaag agtggaaaat 60
 cgtgtggcac gcagcaaattt cttaaaaaat gcttcattaa tcctcgtagg aataactact 120
 ctgagtagatcc ccctcaacat ctatctgatc ataaactaca caataaaaaa aaccacatct 180
 gaatcagaac accacactag ctcaccc acagaatctt acaaaggaaac ttcaacaatc 240
 tctatagaca acccagacat caatccaaac tcacagcatc caactcaaca gtccacagaa 300
 agcctcacac tcagcccccac agcctcggtg agcccatcag aaacagaacc agcatcaaca 360
 tcagacacaa caagccgcctt gtccctcgtt gacagatcca caacacaacc aagtggaaagc 420
 agagcaagggaa caaaaaccgc agtccacaaag aaaaacatcc caagtacagt ttctagaaca 480
 caatccccac tacggcaac aacgaaggcg gtccctcagag ccaccgcctt tcgcacgagc 540
 agcacaggag agggaccaac cacaacatcg gtccagtcgt acagcagcac cacaacccaa 600
 aatcatgaag aaacaggttc agcgaacccca caggcatctg caagcacaat gcaaaacttag 660
 cacaccaaca ttgtaaaacc aaattagttt aaaaaataa tgaaatagtt ctaaagtaaaa 720
 acatgttaggtt gctaacaatc aagaaatccaa aagacaactc ataatctccc taaaacagca 780
 acaacatcatg tcacactttt ctcacatctc cctgggagaaa actttcgccc ccataactgac 840
 aacatcacaac tcacatctcaag aaaagaaaactt gggcaaaaca gcaccaaaa 888

<210> 112

<211> 888

<212> DNA

<213> Human metapneumo virus

<400> 112

atggaggtga aagttagagaa cattcgagca atagacatgc tcaaaggcaag agtggaaaat 60
 cgtgtggcac gtagcaaatg cttaaaaat gcttctttaa tcctcatagg aataactaca 120
 ctgagttatag ccctcaatat ctatctgatc ataaactaca caataaaaaa aaccacatct 180
 gaatcagaac accacactag ctcaccaccc acagaatcta acaaggaaac ttcaacaatc 240
 tccacagaca atccagacat caatccaaac tcacagcatc caactcaaca gtccacagaa 300
 aaccccacac taaacccccgc agcatcggtg agctcatcag aaacagaacc agcatcaaca 360
 ccagacacaa caaacccgcgt gtctccgt a gacaggtcca cagcacaacc aagtggaaagc 420
 agaacaacaaga caaaaaccgc agtccacaca agaaaaacaacc caagcacagc ttccagcaca 480
 caatccccac cacggtaac aacgaaggca atcctcagag ccaccgtt ccgcattgagc 540
 agcacaggaa aaagaccagc cacaacatta gtccagtcg acagcagcac cacaacccca 600
 aatcatgaag aaacagggtc agcaaactca caggcatctg caagcacaat gcaaaactag 660
 cactccaaac atataaaacc aaatttagtta acaaaaaata cgagatagct ctaaagtaaa 720
 acatgttaggc accaacaatc aggaaatcaa aagacaactc acaacccccc taaaacagca 780
 acgacaccat gtcaactttg ctcaaatctc tctgggagaa acttttgc acataactaac 840
 aacatcacaa tcatctcaag aaaagaaact gggcaaaaca gcatccaa 888

<210> 113

<211> 888

<212> DNA

<213> Human metapneumo virus

<400> 113

atggaggtga aagttagagaa cattcgagca atagacatgc tcaaaggcaag agtggaaaat 60
 cgtgtggcac gcagcaaatg cttaaaaat gcttctttaa tcctcatagg aataactact 120
 ctgagttatag ccctcaacat ctatctgatc ataaactaca caataaaaaa aaccacatct 180
 gaatcagaac accacactag ctcaccaccc acagaatcta acaaggaaac ttcaacaatc 240
 tctatagaca actcagacat caatccaaac tcacagcatc caactcaaca gtccacagaa 300
 agcctcacac tcagccccac agcctcggtg agcccatcag aaacagaacc agcatcaaca 360
 tcagacacaa caaacccgcgt gtctccgt a gacagatcca caacacaacc aagtggaaagc 420
 agagcaagaa caaaaaccgc agtccacaaag aaaaacatcc caagtacagt ttctagaaca 480
 caatccccac tacggcaac aacgaaggcg gtcttcagag ccaccgcct tcgcattgagc 540
 agcacaggag agggaccaac cacaacatcg gtccagtcg acagcagcac cacaacccca 600
 aatcatgaag aaacagggtc agcgaaccca caggcatctg caagcacaat gcaaaaccag 660
 cacaccaaca ttgcaaaacc aaatttagtta acaaaaaata tgaaatagtt ctaaagtaaa 720
 acatgttagt gccaacaatc aagaaatcaa aagacaactc acaatctccc taaaacagca 780
 acaacatcat gccaactttg ctcaaatctc cctgggagaa accctcgccc ccataactgac 840
 aacatcacaa tcatctcaag aaaagaaact gggcaaaaca gcacccaa 888

<210> 114

<211> 888

<212> DNA

<213> Human metapneumo virus

<400> 114

atggaggtga aagttagagaa cattcgagca atagacatgc tcaaaggcaag agtggaaaat 60
 cgtgtggcac gcagcaaatg cttaaaaat gcttctttaa tcctcatagg aataactact 120
 ctgagttatag ccctcaatat ctatctgatc ataaactaca caataaaaaa aaccacatct 180
 gaatcagaac accacactag ctcaccaccc acagaatcta acaaggaaac ttcaacaatc 240
 cctatagaca acccagacat caatccaaac tcacagcatc caactcaaca gtccacagaa 300
 agcctcacac tctccccac atcctcggtg agctcatcag aaacagaacc agcatcaaca 360
 ccaggcataa caaacccaccc gtcccttgc gacagatcca caacacaacc aagtggaaagc 420
 agaacaacaaga caaacccggac agtccacaaa aaaaacatct caagtacagt ttctagaaca 480
 cagtccccac cacgacaac agcgaaggcg gtccccagag ccaccgcct tcgcacgagc 540
 agcacaggag aaagaccaac cacaacacca gtccagcccc atagcagcac cacaacacaa 600
 aatcatgaag aaacagggtc agcgaaccca caggcatccg caagcacaat gcaaaaccag 660
 cacaccaaca ttgcaagacc aaatttagtta acaaaaaata tgaaatagct ctaaagtaaa 720
 acatgttagt gccaacaatc aagaaatcaa aagataactc ataatctctc taaaacatca 780

acaacatcat gttaactttg ctcaaacttc tctggagaa acttcgccc ccatactggc 840
 aacatcacaa tcatctcaag aaaagaaaact gggcaaaaca acaccaa 888

<210> 115
 <211> 888
 <212> DNA
 <213> Human metapneumo virus

<400> 115
 atggagggtga aagttagagaa cattcgagca atagacatgc tcaaagcaag agtggaaaat 60
 cgtgtggcac gcagcaaatg cttaaaaat gcttctttaa tcctcatagg aataactact 120
 ctgagtagatccctcaatat ctatctgatc ataaactaca caatacaaaa aaccacatct 180
 gaatcagaac accacactag ctcaccaccc acagaatcta acaagggaaac ttcaacaatc 240
 cctatagaca acccagacat caatccaaac tcacagcatc caactcaaca gtccgcagaa 300
 agcctcacac tctacccac atcctcggtg agctcatcag aaacagaacc agcatcaaca 360
 ccaggcataa caaacccact gtcctttgt a gacagatcca caacacaacc aagtggaaagc 420
 agaacaaga caaacccggac agtccacaaa aaaaacatct caagtacagt ttcttagaaca 480
 cagccccac cacggacaac agcgaaggcg gtccccagag ccaccgcct tcgcacgagc 540
 agcacaggag aaagaccaac cacaacacca gtccagcccg atagcagcac cacaacaccaa 600
 aatcatgaag aaacaggctc agcgaaccca caggcatccg caagcacaat gcaaaaccag 660
 cacaccaaca ttgcaagacc aaatttagttt acaaaaaata tgaaatagct ctaaagtaaa 720
 acatgttagt gccaacaatc aagaaatcaa aagataactc ataatcttc taaaacatca 780
 acaacatcat gttaactttg ctcaaacttc tctggagaa accttcgccc ccatactggc 840
 aacatcacaa tcatctcaag aaaagaaaact gggcaaaaca acaccaa 888

<210> 116
 <211> 888
 <212> DNA
 <213> Human metapneumo virus

<400> 116
 atggagggtga aagttagagaa tattcgagca atagacatgc tcaaagcaag agtggaaaat 60
 cgtgtggcac gcagcaaatg cttaaaaat gcttctttaa tcctcatagg aataactact 120
 ctgagtagatccctcaatat ctatctgatc ataaactaca caatacaaaa aaccacatct 180
 gaatcagaac accacactag ctcaccaccc acagaatcta acaagggaaac ttcaacaatc 240
 cctatagaca acccagacat caatccaaac tcacagcatc caactcaaca gtccacagaa 300
 agcctcacac tctacccac atcctcggtg agctcatcag aaacagaacc agcatcaaca 360
 ccaggcataa caaacccact gtcctttgt a gacagatcca caacacaacc aagtggaaagc 420
 agaacaaga caaacccggac agtccacaaa aaaaacatct caagtacagt ttcttagaaca 480
 cagccccac cacggacaac agcgaaggcg gtccccagag ccaccgcct tcgcacgagc 540
 agcacaggag aaagaccaac cacaacacca gtccagcccg atagcagcac cacaacaccaa 600
 aatcatgaag aaacaggctc agcgaaccca caggcatccg caagcacaat gcaaaaccag 660
 cacaccaaca ttgcaagacc aaatttagttt acaaaaaata tgaaatagct ctaaagtaaa 720
 acatgttagt gccaacaatc aagaaatcaa aagataactc ataatcttc taaaacatca 780
 acaacatcat gttaactttg ctcaaacttc tctggagaa accttcgccc ccatactggc 840
 aacatcacaa tcatctcaag aaaagaaaact gggcaaaaca acacccaa 888

<210> 117
 <211> 888
 <212> DNA
 <213> Human metapneumo virus

<400> 117
 atggagggtga aagttagagaa cattcgagca atagacatgc tcaaagcaag agtggaaaat 60
 cgtgtggcac gttagcaaatg cttaaaaat gcttctttaa tcctcatagg aataactaca 120
 ctgagcatag ccctcaatat ctatctgatc ataaactaca caatacaaca aaccacatct 180
 gaatcagaac accacaccag ctcaccaccc acagaatcca acaagggaaac ttcaacaatc 240
 tccacagaca acccagacat caatccaaac tcacagcatc caactcaaca gtccacagaa 300
 aaccccacac tcaaccccagc agcatcagcg agcccatcag aaacagaatc agcatcaaca 360
 ccagatacaa caaacccgcct gtcctccgt a gacaggtcca cggtacaacc aagtggaaac 420
 agaacaaga caaaaactgac agtccacaca agaaacaacc taagcacagc ctccagtaca 480
 caatccccac cacggcaac aacgaaggca atccgcagag ccaccgcct ccgcacgagc 540

agcacagggaa gaagaccaac cacaacacta gtccagtccg acagcagcac cacaacccaa 600
 aatcatgaag aaacaggctc agcgaaccca caggcatctg caagcacaat gaaaaaccag 660
 cacaccaaca atataaaacc aaatttagtta aaaaaaaaata cgagatagct ctaaagtaaa 720
 acatgttaggc accaacaatc aagaaaccaa aagataactc acaatcccc caaaacagca 780
 acgacaccat gtcagcttg ctcaaattctc tctggagaa acttttgcac acatactaac 840
 aacatcacaa ccatctcaag aaaagaaact gggcaaaaca gcatccaa 888

<210> 118
<211> 888
<212> DNA
<213> Human metapneumo virus

<400> 118
atggaggtga aagtagagaa cattcgagca atagacatgc tcaaagcaag agtggaaaat 60
cgtgtggcac gtagcaaatg cttaaaaat gcttcttta tcctcatagg aataactaca 120
ctgagcatag ccctcaatat ctatctgatc ataaactaca caatacaaaa aaccacatct 180
gaatcagaac accacaccag ctcaccaccc acagaatcca acaaggaagc ttcaacaatc 240
tccacagaca acccagacat caatccaaac tcacagcatc caactcaaca gtccacagaa 300
aaccacacac tcaacccagc agcatcgacg agcccatcag aaacagaatc agcatcaaca 360
ccagatacaa caaaccgcct gtctccgtt gacaggttca cggtacaacc aagtggaaaac 420
agaacaaaaga caaaactgac agtccacaca agaaaacaacc taagcacage ctccagtaca 480
caatccccac cacgggcaac aacgaaggca atccgcagag ccaccaccc cccatgagc 540
agcacagggaa gaagaccaac cacaacacta gtccagtccg acagcagcac cacaacccaa 600
aatcatgaag aaacaggctc agcgaaccca caggcatctg caagcacaat gaaaaaccag 660
cacaccaaca atataaaacc aaatttagtta aaaaaaaaata cgagatagct ctaaagtaaa 720
acatgttaggc accaacaatc aagaaaccaa aagataactc acaatcccc caaaacagca 780
acgacaccat gtcagcttg ctcaaattctc tctggagaa acttttgcac acatactaac 840
aacatcacaa ccatctcaag aaaagaaact gggcaaaaca gcatccaa 888

<210> 119
<211> 901
<212> DNA
<213> Human metapneumo virus

<400> 119
atggaaagtaa gagtggagaa cattcgagcg atagacatgt tcaaagcaaa gataaaaaac 60
cgtataagaa gcagcagggtg ctatagaaaat gctacactga tccttattgg actaacagcg 120
ttaagcatgg cacttaatat tttcctgatc atcgatcatg caacattaag aaacatgatc 180
aaaacagaaaa acttgtctaa catgccgtcg gcagaaccaa gaaaaagac cccaatgacc 240
tccacagcag gccccaaacac caaacccaaat ccacagcaag caacacagtg gaccacagag 300
aactcaacat ccccagtgc aaccccgag ggcacatccat acacaggagc aactcaaaca 360
tcagacacaa cagccccca gcaaaaccaca gacaaacaca cagcaccgt aaaatcaacc 420
aatgaacaga tcacccagac aaccacagag aaaaagacaa tcagagcaac aacccaaaaaa 480
agggaaaaaa gaaaagaaaa cacaaccaa accacaagca cagctgcaac cccaaacaacc 540
aacaccacca accaaatcg aaatgcaagt gagacaatca caacatccga cagacccaga 600
actgacacca caacccaaag cagcgaacag acaacccggg caacagaccc aagctcccc 660
ccacaccatg catagagagg tgcaaaactc aaatgagcac aacacacaaa catccatcc 720
aagttagttaa caaaaacca caaaataacc ttgaaaacca aaaaaccaaa acataaaaccc 780
agacccagaa aaacatagac accatatgga aggttctagc atatgcacca atgagatggc 840
atctgttcat gtatcaatag caccaccatc attcaaggaa taagaagagg cgaaaattta 900
a 901

<210> 120
<211> 901
<212> DNA
<213> Human metapneumo virus

<400> 120
atggaaagtaa gagtggagaa cattcgagcg atagacatgt tcaaagcaaa gataaagaac 60
cgtataagaa gcagcagggtg ctatagaaaat gctacactga tccttattgg actaacagcg 120
ttaagcatgg cacttaatat tttcctgatc attgatcatg caacattaag aaacatgatc 180
aaaacagaaaa acttgtctaa catgccatcg gcagaaccaa gaaaaagac cccaatgacc 240

tccacagcag gcccaagcac cgaacccaat ccacagcaag caacacaatg gaccacagag 300
 aactcaacat ccccagcgc aacccttagag agccatccat acacaggac aacccaaaca 360
 ccagacataa cagctcccc acaaaccaca gacaaacaca cagcactgcc aaaatcaacc 420
 aatgaacaga tcacccagac aaccacagag aaaaagacaa ccagagcaac aacccaaaaaa 480
 agggaaaaag aaaaagaaaa cacaaccac accacaagca cagctgcaac ccaaacaacc 540
 aacaccacca accaaaccag aaatgcaagt gagacaatca caacatccga cagacccaga 600
 attgacacca caacccaaag cagcgatcg acaacccggg caacagaccc aagctcccc 660
 ccacaccatg cacagagtgg tgcaaaaccc aaatgaacac aacacacaaa catctcatcc 720
 aagtagttaa caaaaaatcc caaaataacc ttgaaaacca aaaaaccaa ccacaaactt 780
 agacccagaa aaacatagac actatatgga aggttgagc atatgcacca atgaaatgg 840
 atctgttcat gtatcaatag cgccaccatt attaaggaa taagaagagg caaaaattca 900
 a 901

<210> 121

<211> 860

<212> DNA

<213> Human metapneumo virus

<400> 121

atggaagtaa gagttggagaa cattcgagcg atagacatgt tcaaagcaaa gataaaaaac 60
 cgtataagaa gcagcagggt ctatagaaat gctacactga tccttattgg actaacagcg 120
 ttaagcatgg cacttaatat ttctctgatc atcgatcatg caacattaag aaacatgatc 180
 aaaacagaaa atttgctaa catgcccgg gcagaaccaa gcaaaaagac cccaatgacc 240
 tctacagcag gccccaaacac caaacccaaat ccacagcaag caacacagtg gaccacggag 300
 aactcaacat tcccagcgc aacctcagag ggccatctac acacaggac aactcaaaca 360
 ccagacacaa cagctcctca gcaaaccaca gacaaacaca cagcaactg aaaatcaacc 420
 aatgaacaaa tcacccagac aaccacagag aaaaagacaa ccagagcaac aacccaaaga 480
 agggaaaaag ggaagaaaa cacaaccaa accacaagca cagctgtac ccaaacaacc 540
 aacaccacca accaaatcg aaatgcaagc gagacaatca caacatccga cagacccaga 600
 actgactcca caacccaaag cagcgaaacg acaacccggg caacagaccc aagctcccc 660
 ccacatcatg cacagggaaag tgcaaaaccc aaatgaacac aacacacaaa catcccatcc 720
 aagtagttaa caaaaaatca gacccagaaa aacatagaca ctatatgaa ggtccgagca 780
 tatgcacccg tgaatggc tttgttcatg tatcaatagc gccaccattt ttaaggaaat 840
 aagaagaggc aaaaattca 860

<210> 122

<211> 861

<212> DNA

<213> Human metapneumo virus

<400> 122

atggaagtaa gagttggagaa cattcgagcg atagacatgt tcaaagcaaa gataaaaaac 60
 cgtataagaa gcagcagggt ctatagaaat gctacactga tccttattgg actaacagcg 120
 ttaagcatgg cacttaatat ttctctgatc atcgatcatg caacattaag aaacatgatc 180
 aaaacagaaa atttgctaa catgcccgg gcagaaccaa gcaaaaagac cccaatgacc 240
 tccacagcag gccccaaacac caaacccaaat ccacagcaag caacacagtg gaccacggag 300
 aactcaacat ccccagcgc aaccccgag ggccatctac acacaggac aactcaaaca 360
 ccagacacaa cagctcctca gcaaaccaca gacaaacaca cagcaactg aaaatcaacc 420
 aatgaacaga tcacccagac aaccacagag aaaaagacaa ccagagaaac aacccaaaga 480
 agggaaaaag gaaaagaaaa cacaaccaa accacaagca cagctgcaac ccaaacaacc 540
 aacaccacca accaaatcg aaatgcaagc gagacaatca caacatccga cagacccaga 600
 actgactcca caacccaaag cagcgaaacg acaacccagg caacagaccc aagctcccc 660
 gcacaccatg cacagggaaag tgcaaaaccc aaatgaacac aacacacaaa catcccatcc 720
 aagtagttaa caaaaaatc agacccagaa aaacacagac actatatgga aggtccgagc 780
 atatgcacccg atgaaatggc atctgttcat gtatcaatag caccaccattt attaaggaa 840
 taagaagagg caaaaattca a 861

<210> 123

<211> 860

<212> DNA

<213> Human metapneumo virus

<400> 123

atggaagtaa gagtggagaa cattcgagcg atagacatgt tcaaagcaaa gataaaaaac 60
 cgtataagaa gcagcagggtg ctatagaaat gctacattga tccttattgg actaacagcg 120
 ttaagcatgg cacttaatat ttcttgcattc atcgatcatg caacattaag aaacatgatc 180
 aaaacagaaa atttgctaa catgccaccg gcagaaccaa gcaaaaagac cccaatgacc 240
 tccacagcgag gcctaaacac taaacccat ccacagcaag caacacagtg gaccacggag 300
 aactcaacat ccccagcagc aaccccgag ggcattctac acacaggac aactcaaaca 360
 ccagacacaa cagcttcata gcaaaccaca gacaagcaca cagcactgcc aaaatcaacc 420
 aatgaacaga tcacccagac aaccacagag aaaaagacaa ccagagcaac aacccaaaga 480
 agggaaaaag gaaaagaaaa cacaaccac accacaagca cagctgcaac cccaaacaacc 540
 aacaccacca accaaatcg aaatgcaagc gagacaatca caacatccga cagacccaga 600
 actgactcca caacccaaag cagcgaacag acaacccggg caacagaccc aagctcccc 660
 ccacaccatg cacagggaa tgcaaaaccc aaatgaacac aacacacaaa catccatcc 720
 aagtagttaa caaaaaatca gacccagaaa aacatagaca ctatatggaa ggtccgagca 780
 tatgcaccga tgaatggca tctgttcattg tatcaatagc gccaccattt ttaaggaat 840
 aagaagaggc aaaaattcaa 860

<210> 124

<211> 860

<212> DNA

<213> Human metapneumo virus

<400> 124

atggaagtaa gagtggagaa cattcgagcg atagacatgt tcaaagcaaa gataaaaaac 60
 cgtataagaa gcagcagggtg ctatagaaat gctacactga tccttattgg actaacagcg 120
 ttaagcatgg cacttaatat ttcttgcattc atcgatcatg caacattaag aaacatgatc 180
 aaaacagaaa atttgctaa catgccggcc gcaaccacaa gcaaaaagac cccaatgacc 240
 tccacagcgag gccccaaacac caaaccat ccacagcaag caacacagtg gaccacggag 300
 aactcaacat ccccagcagc aaccccgag ggcattctac acacaggac aactcaaaca 360
 ccagacacaa cagcttcata gcaaaccaca gacaacacca cagcactgcc aaaatcaacc 420
 aatgaacaga tcacccagac aaccacagag aaaaagacaa ccagagcaac aacccaaaga 480
 agggaaaaag gaaaagaaaa cacaaccac accacaagca cagctgcaac cccaaacaacc 540
 aacaccacca accaaatcg aaatgcaatt gagacaatca caacatccga cagacccaga 600
 actgactcca caacccaaag cagcgaacag acaacccggg caacagaccc aagctccac 660
 ccacaccatg cacagggaa tgcaaaaccc aaatgaacac aacacacaaa catccatcc 720
 aagtagttaa caaaaaatca gacccagaaa aacatagaca ctatatggaa ggtccgagca 780
 tatgcaccga tgaatggca tctgttcattg tatcaatagc gccaccattt ttaaggaat 840
 aagaagaggc aagaattcaa 860

<210> 125

<211> 886

<212> DNA

<213> Human metapneumo virus

<400> 125

atggaagtaa gagtggagaa cattcgccca atagacatgt tcaaagcaaa aatgaaaaac 60
 cgtataagaa gtagcaagtg ctatagaaat gctacactga tccttattgg attaacagca 120
 ttaagtatgg cacttaatat ttttttaatc attgattatg caatgttaaa aaacatgacc 180
 aaagtggaa acgtgtttaa tatgccggcc gtagaaccaa gcaagaagac cccaatgacc 240
 tctgcagtag acttaaacac caaaccat ccacagcagg caacacagtg ggccgcagag 300
 gattcaacat ctctagcagc aacctcagag gaccatctac acacaggac aactccaaca 360
 ccagatgcaa cagttctca gcaaaccaca gacgagtaca caacatgct gagatcaacc 420
 aacagacaga ccacccaaac aaccacagag aaaaagccaa cggagcaac aaccaaaaaaa 480
 gaaaccacaa ctgcactac aagcacagct gcaacccaaa cactcaacac taccaaccaa 540
 actagctatg tgagagagc aaccacacca tccggcagat ccagaaacag tgccacaact 600
 caaagcagcg accaaacaac ccaggcagca gaccaagct cccaaaccaca ccatacacag 660
 aaaagcacaa caacaacata caacacagac acatccttc caagtagttt aaaaaaaaaac 720
 tataaaataa tcatgaaaac cgaaaaacta gaaaagttaa ttgtactca gaaaagaaca 780
 caaacactat atgaattgtt tgagcgtata tactaatgaa atagcatctg ttgtgcattc 840
 aataataccca tcattatttta agaaataaga agaagctaaa attcaa 886

<210> 126

<211> 889

<212> DNA

<213> Human metapneumo virus

<400> 126

atggaaatggaa gagtggagaa cattcggaca atagacatgt tcaaagcaaa gatgaaaaac 60
 cgtataagaa gcagcaagtg ctatagaaaat gctacactga tccttattgg actgacagca 120
 ttaagtatgg cacttaatat ttcttgatc atcgattatg caacattaa aaacatgacc 180
 aaagtggAAC actgtgtAA tatGCCGCG gtAgAACCGA gtaAGAACAC CCCAATGACC 240
 tctacagttag actcaaggAC CGGACCCAA CCACAGCAGA CAACACAGTG GACCACAGAG 300
 gattcaacat ctctagcAGC AACCTCAAGAG GACCATCTAC ACACAGGGAC AACTCCAACA 360
 cttagatgCAA cAGTTCTCA GCAAACCCCA GACAAGCACA CAACACCGCT GAGATCAACC 420
 aatggacAGA CCACCCAGAC ACCACAGAG AAAAGCCAA CCAGAGCAAT AGCCAAAAAAA 480
 gaaaccacAA accaaaccAC aAGCACAGCT GCAACCCAA CATTCAACAC CACCAATCAA 540
 accagaaatg gaagagAGAC aaccataACA tCTGCCAGAT CCAGAACGA CGCCACAACt 600
 caaAGCAGCG AACAAACACCC CAAGACAAACA GACCAAGCT CCCAACACAC TCACTGCATA 660
 ataAGCACAa TAACAATATG AACACAAACAC AGACACATCT TCTCCAAGTA GTTAACAAAA 720
 aactataAA TAACCATGAA AACCAAAAAA CTAGAAAAGT AAATTGAAc TCAGAAAAGA 780
 acacAAACAC TAAATGAATT GTTGTAGCAT ATATACTAA GAAATAGCAT CTGTTCATGC 840
 atcaataATAA CCATCATTAC TTAAGAAATA AGAAGAAGCA AAAATTCAA 889

<210> 127

<211> 885

<212> DNA

<213> Human metapneumo virus

<400> 127

atggaaatggaa gagtggagaa cattcggca atagacatgt tcaaagcaaa gatgaaaaac 60
 cgtataagaa gtagcaagtg ctatagaaaat gctacactga tccttattgg attaACAGCA 120
 ttaagtatgg cacttaatat ttTTTAATC attgattatg caatgttAA aaacatgacc 180
 aaagtggAAC actgtgtAA tatGCCGCG gtAgAACCAA gcaAGAACAC CCCAATGACC 240
 tctgcAGTAG ACTTAAACAC CAAACTCAAT CCACAGCAGG CAACACAGTT GACCACAGAG 300
 gattcaacat ctctagcAGC AACCTCGGAG GATCATTAC TCACAGGGAC AACTCCAACA 360
 ccAGATGCAA CAGTCTCTCA GCAAACCCACA GACGAGCACA CAACACTGCT GAGATCAACC 420
 AACAGACAGA CCACCCAAAC AACCCACAGAG AAAAGCCAA CGGAGCAAC AACCAAAAAAA 480
 gaaaccacAA cTCGAACAC AACGCACAGCT GCAACCCAA CACTCAACAC CACCAACCAA 540
 actAGCAATG gaagagAGC AACCCACAA TCCACCAAGAT CCAGAACCGG TGCCACAACt 600
 caAAACAGCG ATCAAACAC CTAGACAGCA GACCAAGCT CCCAACACAC CCATACACAG 660
 AAAAGCACAa CAACACACAT CAACACAGAC ACATTTCTC CAAGTAGTT ACAAAAAACt 720
 atAAAATAAC CATGAAAAct AAAAGTTAAT TTGAACCTAG AAAAGAACAC 780
 AACACACTATA TGAATTGTT GAGCGTATAT ACTAATGAAA TAGCATCTGT TTGTGCACTCA 840
 ATAATACCAT CATTATTTAA GAAATAAGAA GAAGCTAAA TTCAA 885

<210> 128

<211> 885

<212> DNA

<213> Human metapneumo virus

<400> 128

atggaaatggaa gagtggagaa cattcggca atagacatgt tcaaagcaaa gatgaaaaac 60
 cgcataagaa gtagcaagtg ctatagaaaat gctacactga tccttattgg attaACAGCA 120
 ttaagtatgg cacttaatat ttTTTAATC attgattatg caacattAA aaacatgacc 180
 aaagtggAAC actgtgtAA tatGCCGCG gtAgAACCAA gcaAGAACAC CCCAATGACC 240
 tctgcAGTAG ACTTAAACAC CAAACTCAAT CCACAGCAGG CAACACAGTT GACCACAGAG 300
 gattcaacat ctctagcAGC AACCTCAAGAG GGCATCCAC ACACAGGAAC AACTCCAACA 360
 ccAGACGCAA CAGTCTCTCA GCAAACCCACA GACGAGCACA CAACACTGCT GAGATCAACC 420
 AACAGACAGA CCACCCAAAC AGCCACAGAG AAAAGCCAA CTGGAGCAAC AACCAAAAAAA 480
 gaaaccacAA CCCGAACTAC AAGTACAGCT GCAACCCAA CACCCACAC CACCAACCAA 540
 accAGCAATG gaagagAGC AACCCACAA TCCGCCAGGT CGAGAACCGG TGCCACAACt 600
 caAAACAGCG ATCAAATAAC CCAGGCAGCA GACTCAAGCT CCCAACACAC CCATACACAG 660
 AAAAGCACAa CAACAGCATA CAACACAGAC ACATTTCTC CAAGTAGTT ACAAAAAACt 720
 atAAAATAAC CATGAAAACC AAAAGTTAAT TTGAACCTAG AAAAGAACAC 780

aaacactata tgaattgttt gagcgtatat actaatgaaa tagcatctgt ttgtgcata 840
 ataataccat cattattaa gaaataagaa gaagctaaaa ttcaa 885

<210> 129
 <211> 886
 <212> DNA
 <213> Human metapneumo virus

<400> 129
 atggaagtaa gagtggagaa cattcgccca atagacatgt tcaaagcaaa gataaaaaac 60
 cgtataagaa gtagcaagtg ctatagaaat gctacactga tccttattgg attaacagca 120
 ctaagtatgg cacttaatat ttttttaatc attgattatg caaatcaaa aacatgacc 180
 aaagtggAAC actgtgttaa tatgccggcgtt gtagaaccAA gcaagaagAC cccaatgacc 240
 tctgcagtag actcaaACAC caaacCCAA ccacAGCAGG caacacAGTT gaccACAGAG 300
 gattctacat cttagcAGC aaccCTAGAG gaccatCCAC acacAGGGAC aactCCAACA 360
 ccagatgCAA cagtCTCTCA gcaaACCACCA gacGAGCACA caacACTGCT gagatCAACC 420
 aacagacAGA ccacCCAAAC aactGCAGAG AAAAGCCAA ccaggGCCAC aaccAAAAAA 480
 gaaaccACAA ctcgaACCAC aagcACAGCT gcaacCCAA CACTCAACAC caccAACAA 540
 actagcaATG gaagAGAGGC aaccACACCA tctGCCAGAT ccagAAACAA tgccACAAct 600
 caaAGCAGCG atcaACACAC ccaggCAGCA gaacCAAGCT cccaaTCACA acataCACAG 660
 aaaAGCACAA caacaACATA caacACAGAC acatTTCTC taagtGTtTA acaaaaaAAAC 720
 tataAAATAA ccatgAAAAC caaaaaACTA gaaaAGTTA ttGAACTCA gaaaAGAAACA 780
 caaacactat atgaattatt tgagcgtata tactaatgaa atagcatCTG ttGTCATC 840
 aataataccat tcattattta agaaATAAGA agaAGCTAA attCAA 886

<210> 130
 <211> 887
 <212> DNA
 <213> Human metapneumo virus

<400> 130
 atggaagtaa gagtggagaa cattcgccca atagacatgt tcaaagcaaa gataaaaaac 60
 cgtataagaa gtagcaagtg ctatagaaat gctacactga tccttattgg attatCAGCA 120
 ctaagtatgg cacttaatat ttttttaatc attgattatg caaatcaaa aacatgacc 180
 agagtggAAC actgtgtCAA tatGCCGGCgtt gtagaaccAA gcaagaagAC cccaatgacc 240
 tctgcagtag acttAAACAC caaacCCAA ccacAGCAGG caacacAGTT gaccACAGAG 300
 gattcaacat ctctAGCAGC aaccCTAGAG ggCCATCTAC acacAGGGAC aactCCAACA 360
 ccagatgtAA cagtCTCTCA gcaaACCACCA gacGAGCACA caacACTGCT gagatCAACC 420
 aacagacAGA ccacCCAAAC agCCGAGAG AAAAGCCAA ccagAGTAAC aactAACAAA 480
 gaaaccATAA ctcgaACCAC aagcACAGCC gcaacCCAA CACTCAACAC caccAACAA 540
 accaacaATG gaagAGAGGC aaccACACCA tctGCCAGAT ccagAAACAA tgccACAAct 600
 caaAGCAGCG accAAACAAAC ccaggCAGCA gacCCAAAGCT cccaaTCACA acataCACAG 660
 aaaAGCATAA caacaACATA caacACAGAC acatTTCTC caagtGTtTA acaaaaaAAAC 720
 tataAAATAA ccatgAAAAC caaaaaACTA agaaaAGTTA attGAACTC gaaaAGAAAC 780
 acaaACACTA tatgaATTGT ttGAGCgtAT atactaatgA aatAGCATCT GttGTCATC 840
 caataataccat atcattattt aagaATTAAG aagaAGCTAA aattCAA 887

<210> 131
 <211> 887
 <212> DNA
 <213> Human metapneumo virus

<400> 131
 atggaagtaa gagtggagaa cattcgccca atagacatgt tcaaagcaaa gataaaaaac 60
 cgtataagaa gtagcaagtg ctatagaaat gctacactga tccttattgg attatCAGCA 120
 ctaagtatgg cacttaatat ttttttaatc attgattatg caaatcaaa aacatgacc 180
 agagtggAAC actgtgtCAA tatGCCGGCgtt gtagaaccAA gcaagaagAC cccaatgacc 240
 tctgcagtag acttAAACAC caaacCCAA ccacAGCAGG caacacAGTT gaccACAGAG 300
 gattcaacat ctccAGCAGC aaccCTAGAG ggCCATCTAC acacAGGGAC aactCCAACA 360
 ccagatgCAA cagtCTCTCA gcaaACCACCA gacGAGCACA caacACTGCT gagatCAACC 420
 aacagacAGA ccacCCAAAC aacCGAGAG AAAAGCCAA ccagAGCAAC aaccAAAAAA 480
 gaaaccATAA ctcgaACCAC aagcACAGCT gcaacCCAA CACTCAACAC caccAACAA 540

accagcaatg gaagagaggc aaccacaaca tctgccagat ccagaaacaa tgccacaact 600
 caaagcagcg accaaacaac ccaggcagca gacccaagct cccaatcaca acatacaaag 660
 aaaagcacaa caacaacata caacacagac acatcttctc caagtagtta aaaaaaaaaac 720
 tataaaaataa ccatgaaaac caaaaaaaaact agaaaaagtta atttgaactc agaaaagaac 780
 acaaacacta tatgaattgt ttgagcgtat atactaatga aatagcatct gtttgtcat 840
 caataatacc atcattattt aagaattaag aagaagctaa aattcaa 887

<210> 132

<211> 886

<212> DNA

<213> Human metapneumo virus

<400> 132

atgaaagtaa gagtggagaa cattcgggca atagacatgt tcaaagcaaa gataaaaaac 60
 cgtataagaa gtagcaagtg ctatagaaat gctacactga tccttattgg attaacagca 120
 ctaagtatgg cacttaatat tttttttaatc attgattatg caacataaaa aaacatgacc 180
 aaagtggAAC actgtgttaa tatGCCGCG gtagaaccaa gcaagaagac cccaatgacc 240
 tctgcagtag acttaaacac caaacccaaat ccacagcagg caacacagt gaccacagag 300
 gactctacat cttagcagc aacccttagag gaccatccac acacaggac aactccaaca 360
 ccagatgcaa cagtcctca gcaaaccaca gacgacaca caacactgt gagatcaacc 420
 aacagacaga ccacccaaac aactgcagag aaaaagccaa ccagagcaac aaccaaaaaaa 480
 gaaaccacaa ctcgaaccac aagcacagct gcaacccaaa cactcaacac caccaaccaa 540
 actagcaatg gaagagaggc aaccacaaca tctgccagat ccagaaacaa tgccacaact 600
 caaagcagcg atcaaacaac ccaagcagca gaaccaact cccaatcaca acatacacag 660
 aaaagcacaa caacaacata caacacagac acatcttctc taagtagtta aaaaaaaaaac 720
 tataaaaataa ccatgaaaac caaaaaaaaact gaaaaagttaa tttgaactca gaaaggaaca 780
 caaacactat atgaattatt tgagcgtata tactaatgaa atagcatctg tttgtgcac 840
 aataatacca tcattattta agaaataaga agaagctaaa attcaa 886

<210> 133

<211> 236

<212> PRT

<213> Human metapneumo virus

<400> 133

Met	Glu	Val	Lys	Val	Glu	Asn	Ile	Arg	Thr	Ile	Asp	Met	Leu	Lys	Ala
1				5					10				15		
Arg	Val	Lys	Asn	Arg	Val	Ala	Arg	Ser	Lys	Cys	Phe	Lys	Asn	Ala	Ser
				20					25				30		
Leu	Val	Leu	Ile	Gly	Ile	Thr	Thr	Leu	Ser	Ile	Ala	Leu	Asn	Ile	Tyr
				35				40				45			
Leu	Ile	Ile	Asn	Tyr	Lys	Met	Gln	Lys	Asn	Thr	Ser	Glu	Ser	Glu	His
				50			55				60				
His	Thr	Ser	Ser	Ser	Pro	Met	Glu	Ser	Ser	Arg	Glu	Thr	Pro	Thr	Val
				65		70			75				80		
Pro	Thr	Asp	Asn	Ser	Asp	Thr	Asn	Ser	Ser	Pro	Gln	His	Pro	Thr	Gln
				85				90				95			
Gln	Ser	Thr	Glu	Gly	Ser	Thr	Leu	Tyr	Phe	Ala	Ala	Ser	Ala	Ser	Ser
				100			105					110			
Pro	Glu	Thr	Glu	Pro	Thr	Ser	Thr	Pro	Asp	Thr	Thr	Asn	Arg	Pro	Pro
				115			120				125				
Phe	Val	Asp	Thr	His	Thr	Thr	Pro	Pro	Ser	Ala	Ser	Arg	Thr	Lys	Thr
				130			135				140				
Ser	Pro	Ala	Val	His	Thr	Lys	Asn	Asn	Pro	Arg	Thr	Ser	Ser	Arg	Thr
				145		150				155				160	
His	Ser	Pro	Pro	Arg	Ala	Thr	Thr	Arg	Thr	Ala	Arg	Arg	Thr	Thr	Thr
				165				170				175			
Leu	Arg	Thr	Ser	Ser	Thr	Arg	Lys	Arg	Pro	Ser	Thr	Ala	Ser	Val	Gln
				180			185				190				
Pro	Asp	Ile	Ser	Ala	Thr	Thr	His	Lys	Asn	Glu	Glu	Ala	Ser	Pro	Ala
				195			200				205				
Ser	Pro	Gln	Thr	Ser	Ala	Ser	Thr	Thr	Arg	Ile	Gln	Arg	Lys	Ser	Val

210	215	220
Glu Ala Asn Thr Ser	Thr Thr Tyr Asn Gln	Thr Ser
225	230	235

<210> 134
<211> 236
<212> PRT
<213> Human metapneumo virus

<400> 134

Met	Glu	Val	Lys	Val	Glu	Asn	Ile	Arg	Thr	Ile	Asp	Met	Leu	Lys	Ala
1	5								10						15
Ser	Val	Lys	Asn	Arg	Val	Ala	Arg	Ser	Lys	Cys	Phe	Lys	Asn	Ala	Ser
	20							25						30	
Leu	Val	Leu	Ile	Gly	Ile	Thr	Thr	Leu	Ser	Ile	Ala	Leu	Asn	Ile	Tyr
	35					40				45					
Leu	Ile	Ile	Asn	Tyr	Lys	Met	Gln	Lys	Asn	Thr	Ser	Glu	Ser	Glu	His
	50					55				60					
His	Thr	Ser	Ser	Pro	Met	Glu	Ser	Ser	Arg	Glu	Thr	Pro	Thr	Val	
	65				70			75				80			
Pro	Thr	Asp	Asn	Ser	Asp	Thr	Asn	Ser	Ser	Pro	Gln	His	Pro	Thr	Gln
		85					90				95				
Gln	Ser	Thr	Glu	Gly	Ser	Thr	Leu	Tyr	Phe	Ala	Ala	Ser	Ala	Ser	Ser
		100				105				110					
Pro	Glu	Thr	Glu	Pro	Thr	Ser	Thr	Pro	Asp	Thr	Thr	Asn	Arg	Pro	Pro
	115					120				125					
Phe	Val	Asp	Thr	His	Thr	Thr	Pro	Pro	Ser	Ala	Ser	Arg	Thr	Lys	Thr
	130					135				140					
Ser	Pro	Ala	Val	His	Thr	Lys	Asn	Asn	Pro	Arg	Thr	Ser	Ser	Arg	Thr
	145					150				155				160	
His	Ser	Pro	Pro	Arg	Ala	Thr	Thr	Arg	Thr	Ala	Arg	Arg	Thr	Thr	Thr
		165					170				175				
Leu	Arg	Thr	Ser	Thr	Arg	Lys	Arg	Pro	Ser	Thr	Ala	Ser	Val	Gln	
		180				185				190					
Pro	Asp	Ile	Ser	Ala	Thr	Thr	His	Lys	Asn	Glu	Glu	Ala	Ser	Pro	Ala
	195					200				205					
Ser	Pro	Gln	Thr	Ser	Ala	Ser	Thr	Thr	Arg	Ile	Gln	Arg	Lys	Ser	Val
	210					215				220					
Glu	Ala	Asn	Thr	Ser	Thr	Thr	Tyr	Asn	Gln	Thr	Ser				
	225					230				235					

<210> 135
<211> 236
<212> PRT
<213> Human metapneumo virus

<400> 135

Met	Glu	Val	Lys	Val	Glu	Asn	Ile	Arg	Thr	Ile	Asp	Met	Leu	Lys	Ala
1	5								10						15
Arg	Val	Lys	Asn	Arg	Val	Ala	Arg	Ser	Lys	Cys	Phe	Lys	Asn	Ala	Ser
	20						25						30		
Leu	Val	Leu	Ile	Gly	Ile	Thr	Thr	Leu	Ser	Ile	Ala	Leu	Asn	Ile	Tyr
	35					40				45					
Leu	Ile	Ile	Asn	Tyr	Lys	Met	Gln	Lys	Asn	Thr	Ser	Glu	Ser	Glu	His
	50					55				60					
His	Thr	Ser	Ser	Pro	Met	Glu	Ser	Ser	Arg	Glu	Thr	Pro	Thr	Val	
	65				70			75				80			
Pro	Thr	Asp	Asn	Ser	Asp	Thr	Asn	Ser	Ser	Pro	Gln	His	Pro	Thr	Gln
		85				90				95					
Gln	Ser	Thr	Glu	Gly	Ser	Thr	Leu	Tyr	Phe	Ala	Ala	Ser	Ala	Asn	Ser

100	105	110
Pro Glu Thr Glu Pro Thr Ser Thr Pro Asp Thr Thr Asn Arg Pro Pro		
115	120	125
Phe Val Asp Thr His Thr Thr Pro Pro Ser Ala Ser Arg Thr Lys Thr		
130	135	140
Ser Pro Ala Val His Thr Lys Asn Asn Pro Arg Ile Ser Ser Arg Thr		
145	150	155
His Ser Pro Pro Trp Ala Thr Thr Arg Thr Ala Arg Arg Thr Thr Thr		
165	170	175
Leu Arg Thr Ser Thr Arg Lys Arg Pro Ser Thr Ala Ser Ala Gln		
180	185	190
Pro Asp Ile Ser Ala Thr Thr His Lys Asn Glu Glu Ala Ser Pro Ala		
195	200	205
Ser Pro Gln Thr Ser Ala Ser Thr Thr Arg Thr Gln Arg Lys Ser Val		
210	215	220
Glu Ala Asn Thr Ser Thr Tyr Asn Gln Thr Ser		
225	230	235

<210> 136

<211> 236

<212> PRT

<213> Human metapneumo virus

<400> 136

Met Glu Val Lys Val Glu Asn Ile Arg Thr Ile Asp Met Leu Lys Ala			
1	5	10	15
Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser			
20	25	30	
Leu Val Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr			
35	40	45	
Leu Ile Ile Asn Tyr Lys Met Gln Lys Asn Thr Ser Glu Ser Glu His			
50	55	60	
His Thr Ser Ser Ser Pro Met Glu Ser Ser Arg Glu Thr Pro Thr Val			
65	70	75	80
Pro Thr Asp Asn Ser Asp Thr Asn Ser Ser Pro Gln His Pro Thr Gln			
85	90	95	
Gln Ser Thr Glu Gly Ser Thr Leu Tyr Phe Ala Ala Ser Ala Asn Ser			
100	105	110	
Pro Glu Thr Glu Pro Thr Ser Thr Pro Asp Thr Thr Asp Arg Pro Pro			
115	120	125	
Phe Val Asp Thr His Thr Thr Pro Pro Ser Ala Ser Arg Thr Lys Thr			
130	135	140	
Ser Pro Ala Val His Thr Lys Asn Asn Pro Arg Ile Ser Ser Arg Thr			
145	150	155	160
His Ser Pro Pro Trp Ala Thr Thr Arg Thr Ala Arg Arg Thr Thr Thr			
165	170	175	
Leu Arg Thr Ser Ser Thr Arg Lys Arg Pro Ser Thr Ala Ser Val Gln			
180	185	190	
Pro Asp Ile Ser Ala Thr Thr His Lys Asn Glu Glu Ala Ser Pro Ala			
195	200	205	
Ser Pro Gln Thr Ser Ala Ser Thr Thr Arg Thr Gln Arg Lys Ser Val			
210	215	220	
Glu Ala Asn Thr Ser Thr Tyr Asn Gln Thr Ser			
225	230	235	

<210> 137

<211> 236

<212> PRT

<213> Human metapneumo virus

<400> 137

Met Glu Val Lys Val Glu Asn Ile Arg Thr Ile Asp Met Leu Lys Ala
 1 5 10 15
 Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
 20 25 30
 Leu Val Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
 35 40 45
 Leu Ile Ile Asn Tyr Lys Met Gln Lys Asn Thr Ser Glu Ser Glu His
 50 55 60
 His Thr Ser Ser Ser Pro Met Glu Ser Ser Arg Glu Thr Pro Thr Val
 65 70 75 80
 Pro Thr Asp Asn Ser Asp Thr Asn Ser Ser Pro Gln His Pro Thr Gln
 85 90 95
 Gln Ser Thr Glu Gly Ser Thr Leu Tyr Phe Ala Ala Ser Ala Ser Ser
 100 105 110
 Pro Glu Thr Glu Pro Thr Ser Thr Pro Asp Thr Thr Asp Arg Pro Pro
 115 120 125
 Phe Val Asp Thr His Thr Thr Pro Pro Ser Ala Ser Arg Thr Lys Thr
 130 135 140
 Ser Pro Ala Val His Thr Lys Asn Asn Pro Arg Ile Ser Ser Arg Thr
 145 150 155 160
 His Ser Pro Pro Trp Ala Thr Thr Arg Thr Ala Arg Arg Thr Thr Thr
 165 170 175
 Leu Arg Thr Ser Ser Thr Arg Lys Arg Pro Ser Thr Ala Ser Val Gln
 180 185 190
 Pro Asp Ile Ser Ala Thr Thr His Lys Asn Glu Glu Ala Ser Pro Ala
 195 200 205
 Ser Pro Gln Thr Ser Ala Ser Thr Thr Arg Thr Gln Arg Lys Ser Val
 210 215 220
 Glu Ala Asn Thr Ser Thr Thr Tyr Asn Gln Thr Ser
 225 230 235

<210> 138

<211> 236

<212> PRT

<213> Human metapneumo virus

<400> 138

Met Glu Val Lys Val Glu Asn Ile Arg Thr Ile Asp Met Leu Lys Ala
 1 5 10 15
 Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
 20 25 30
 Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
 35 40 45
 Leu Ile Ile Asn Tyr Thr Met Gln Glu Asn Thr Ser Glu Ser Glu His
 50 55 60
 His Thr Ser Ser Ser Pro Met Glu Ser Ser Arg Glu Thr Pro Thr Val
 65 70 75 80
 Pro Ile Asp Asn Ser Asp Thr Asn Pro Gly Ser Gln Tyr Pro Thr Gln
 85 90 95
 Gln Ser Thr Glu Asp Ser Thr Leu His Ser Ala Ala Ser Ala Ser Ser
 100 105 110
 Pro Glu Thr Glu Pro Thr Ser Thr Pro Asp Thr Thr Ser Arg Pro Pro
 115 120 125
 Phe Val Asp Thr His Thr Thr Pro Pro Ser Ala Ser Arg Thr Arg Thr
 130 135 140
 Ser Pro Ala Val His Thr Lys Asn Asn Pro Arg Val Ser Pro Arg Thr
 145 150 155 160
 His Ser Pro Pro Trp Ala Met Thr Arg Thr Val Arg Gly Thr Thr Thr
 165 170 175
 Leu Arg Thr Ser Ser Thr Arg Lys Arg Leu Ser Thr Ala Ser Val Gln

180	185	190
Pro Asp Ser Ser Ala Thr Thr His Lys His Glu Glu Thr Ser Pro Val		
195	200	205
Ser Pro Gln Thr Ser Ala Ser Thr Ala Arg Pro Gln Arg Lys Gly Met		
210	215	220
Glu Ala Ser Thr Ser Thr Tyr Asn Gln Thr Ser		
225	230	235

<210> 139
<211> 236
<212> PRT
<213> Human metapneumo virus

<400> 139	139		
Met Glu Val Lys Val Glu Asn Ile Arg Thr Ile Asp Met Leu Lys Ala			
1	5	10	15
Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser			
20	25	30	
Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr			
35	40	45	
Leu Ile Ile Asn Tyr Thr Met Gln Glu Asn Thr Ser Glu Ser Glu His			
50	55	60	
His Thr Ser Ser Pro Met Glu Ser Ser Arg Glu Thr Pro Thr Val			
65	70	75	80
Pro Met Asp Asn Ser Asp Thr Asn Pro Gly Ser Gln Tyr Pro Thr Gln			
85	90	95	
Gln Ser Thr Glu Gly Ser Thr Leu His Phe Ala Ala Ser Ala Ser Ser			
100	105	110	
Pro Glu Thr Glu Pro Thr Ser Thr Pro Asp Thr Thr Ser Arg Pro Pro			
115	120	125	
Phe Val Asp Thr His Thr Thr Pro Ser Ser Ala Ser Arg Thr Lys Thr			
130	135	140	
Ser Pro Ala Val His Thr Lys Asn Asn Leu Arg Ile Ser Pro Arg Thr			
145	150	155	160
His Ser Pro Pro Trp Ala Met Thr Arg Thr Val Arg Gly Thr Thr Thr			
165	170	175	
Leu Arg Thr Ser Ser Ile Arg Lys Arg Pro Ser Thr Ala Ser Val Gln			
180	185	190	
Pro Asp Ser Ser Ala Thr Thr His Lys His Glu Glu Ala Ser Pro Val			
195	200	205	
Ser Pro Gln Ala Ser Ala Ser Thr Ala Arg Pro Gln Arg Lys Gly Met			
210	215	220	
Glu Ala Ser Thr Ser Thr Tyr Asn Gln Thr Ser			
225	230	235	

<210> 140
<211> 236
<212> PRT
<213> Human metapneumo virus

<400> 140	140		
Met Glu Val Lys Val Glu Asn Ile Arg Thr Ile Asp Met Leu Lys Ala			
1	5	10	15
Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser			
20	25	30	
Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr			
35	40	45	
Leu Ile Ile Asn Tyr Thr Met Gln Glu Asn Thr Ser Glu Ser Glu His			
50	55	60	
His Thr Ser Ser Pro Met Glu Ser Ser Arg Glu Thr Pro Thr Val			

65	70	75	80
Pro Met Asp Asn Ser Asp Thr Asn Pro Gly Ser Gln Tyr Pro Thr Gln			
85	90	95	
Gln Ser Thr Glu Gly Ser Thr Leu His Phe Ala Ala Ser Ala Ser Ser			
100	105	110	
Pro Glu Thr Glu Pro Thr Ser Thr Pro Asp Thr Thr Ser Arg Pro Pro			
115	120	125	
Phe Val Asp Thr His Thr Thr Pro Ser Ser Ala Ser Arg Ile Arg Thr			
130	135	140	
Ser Pro Ala Val His Thr Lys Asn Asn Leu Arg Ile Ser Pro Arg Thr			
145	150	155	160
His Ser Pro Pro Trp Ala Met Thr Arg Thr Val Arg Gly Thr Thr Thr			
165	170	175	
Leu Arg Thr Ser Ser Ile Arg Lys Arg Pro Ser Thr Ala Ser Val Gln			
180	185	190	
Pro Asp Ser Ser Ala Thr Thr His Lys His Glu Glu Ala Ser Pro Val			
195	200	205	
Ser Pro Gln Ala Ser Ala Ser Thr Ala Arg Pro Gln Arg Lys Gly Met			
210	215	220	
Glu Ala Ser Thr Ser Thr Tyr Asn Gln Thr Ser			
225	230	235	

<210> 141

<211> 228

<212> PRT

<213> Human metapneumovirus

<220>

<221> VARIANT

<222> 220

<223> Xaa = unknown amino acid or other

<400> 141

Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala			
1	5	10	15
Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser			
20	25	30	
Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr			
35	40	45	
Leu Ile Ile Asn Tyr Thr Ile Gln Lys Thr Ser Glu Ser Glu His			
50	55	60	
His Thr Ser Ser Pro Pro Thr Glu Pro Asn Lys Glu Ala Ser Thr Ile			
65	70	75	80
Ser Thr Asp Asn Pro Asp Ile Asn Pro Ser Ser Gln His Pro Thr Gln			
85	90	95	
Gln Ser Thr Glu Asn Pro Thr Leu Asn Pro Ala Ala Ser Ala Ser Pro			
100	105	110	
Ser Glu Thr Glu Pro Ala Ser Thr Pro Asp Thr Thr Asn Arg Leu Ser			
115	120	125	
Ser Val Asp Arg Ser Thr Ala Gln Pro Ser Glu Ser Arg Thr Lys Thr			
130	135	140	
Lys Pro Thr Val His Thr Ile Asn Asn Pro Asn Thr Ala Ser Ser Thr			
145	150	155	160
Gln Ser Pro Pro Arg Thr Thr Lys Ala Ile Arg Arg Ala Thr Thr			
165	170	175	
Phe Arg Met Ser Ser Thr Gly Lys Arg Pro Thr Thr Thr Leu Val Gln			
180	185	190	
Ser Asp Ser Ser Thr Thr Gln Asn His Glu Glu Thr Gly Ser Ala			
195	200	205	
Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Asn Xaa His Thr Asn Asn			
210	215	220	

Ile Lys Pro Asn
225

<210> 142
<211> 228
<212> PRT
<213> Human metapneumo virus

<400> 142
Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala
1 5 10 15
Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
20 25 30
Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
35 40 45
Leu Ile Ile Asn Tyr Thr Ile Gln Lys Thr Thr Ser Glu Ser Glu His
50 55 60
His Thr Ser Ser Pro Pro Thr Glu Ser Asn Lys Glu Thr Ser Thr Ile
65 70 75 80
Pro Ile Asp Asn Pro Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln
85 90 95
Gln Ser Thr Glu Ser Pro Thr Leu Asn Pro Ala Ala Ser Val Ser Pro
100 105 110
Ser Glu Thr Glu Pro Ala Ser Thr Pro Asp Thr Thr Asn Arg Leu Ser
115 120 125
Ser Val Asp Arg Ser Thr Thr Gln Pro Ser Glu Ser Arg Thr Lys Thr
130 135 140
Lys Pro Thr Val His Thr Lys Asn Asn Pro Ser Thr Val Ser Arg Thr
145 150 155 160
Gln Ser Pro Leu Arg Ala Thr Thr Lys Ala Val Leu Arg Ala Thr Ala
165 170 175
Phe Arg Thr Ser Ser Thr Arg Lys Arg Pro Thr Thr Ser Val Gln
180 185 190
Ser Asp Ser Ser Thr Thr Gln Asn His Glu Glu Thr Ser Ser Ala
195 200 205
Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Ser Gln His Thr Asn Asn
210 215 220
Ile Lys Pro Asn
225

<210> 143
<211> 228
<212> PRT
<213> Human metapneumo virus

<400> 143
Met Glu Val Lys Val Glu Asn Ile Arg Ala Val Asp Met Leu Lys Ala
1 5 10 15
Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
20 25 30
Leu Ile Leu Val Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
35 40 45
Leu Ile Val Asn Tyr Thr Ile Gln Lys Thr Thr Ser Glu Ser Glu His
50 55 60
His Thr Ser Ser Ser Pro Thr Glu Ser Asn Lys Gly Thr Ser Thr Ile
65 70 75 80
Pro Thr Asp Asn Pro Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln
85 90 95
Gln Ser Thr Glu Ser Pro Thr Leu Asn Thr Ala Ala Ser Val Ser Pro
100 105 110

Ser Glu Thr Glu Pro Ala Ser Thr Pro Asp Thr Thr Asn Arg Leu Ser
 115 120 125
 Ser Ala Asp Arg Ser Thr Thr Gln Pro Ser Glu Ser Arg Thr Lys Thr
 130 135 140
 Lys Leu Thr Val His Thr Lys Asn Asn Leu Ser Thr Ala Ser Arg Thr
 145 150 155 160
 Gln Ser Pro Pro Arg Ala Thr Thr Lys Ala Val Leu Arg Asp Thr Ala
 165 170 175
 Phe His Thr Ser Ser Thr Gly Lys Arg Pro Thr Thr Ser Val Gln
 180 185 190
 Ser Gly Ser Ser Thr Thr Gln Asn His Glu Glu Thr Ser Ser Ser
 195 200 205
 Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Asp Gln Asp Thr Asn Asn
 210 215 220
 Thr Lys Gln Asn
 225

<210> 144
 <211> 228
 <212> PRT
 <213> Human metapneumo virus

<220>
 <221> VARIANT
 <222> 81
 <223> Xaa = Any Amino Acid

<400> 144
 Met Glu Val Lys Val Glu Asn Ile Arg Ala Val Asp Met Leu Lys Ala
 1 5 10 15
 Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
 20 25 30
 Leu Ile Leu Val Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
 35 40 45
 Leu Ile Val Asn Tyr Thr Ile Gln Lys Thr Thr Ser Glu Ser Glu His
 50 55 60
 His Thr Ser Ser Ser Pro Thr Glu Ser Asn Lys Gly Thr Ser Thr Ile
 65 70 75 80
 Xaa Thr Asp Asn Pro Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln
 85 90 95
 Gln Ser Thr Glu Ser Pro Thr Leu Asn Thr Ala Ala Ser Val Ser Pro
 100 105 110
 Ser Glu Thr Glu Pro Ala Ser Thr Pro Asp Thr Thr Asn Arg Leu Ser
 115 120 125
 Ser Ala Asp Arg Ser Thr Thr Gln Pro Ser Glu Ser Arg Thr Lys Thr
 130 135 140
 Lys Leu Thr Val His Thr Lys Asn Asn Leu Ser Thr Ala Ser Arg Thr
 145 150 155 160
 Gln Ser Pro Pro Arg Ala Thr Thr Lys Ala Val Leu Arg Asp Thr Ala
 165 170 175
 Phe His Thr Ser Ser Thr Gly Lys Arg Pro Thr Thr Ser Val Gln
 180 185 190
 Ser Gly Ser Ser Thr Thr Gln Asn His Glu Glu Thr Ser Ser Ser
 195 200 205
 Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Asp Gln Asp Thr Asn Asn
 210 215 220
 Thr Lys Gln Asn
 225

<210> 145

<211> 228
<212> PRT
<213> Human metapneumovirus

<220>
<221> VARIANT
<222> 220
<223> Xaa = unknown amino acid or other

<400> 145
Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala
1 5 10 15
Arg Met Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
20 25 30
Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
35 40 45
Leu Ile Ile Asn Tyr Thr Ile Gln Lys Thr Thr Ser Glu Ser Glu His
50 55 60
His Thr Ser Ser Pro Pro Thr Glu Ser Asn Lys Glu Thr Ser Thr Ile
65 70 75 80
Pro Ile Asp Asn Pro Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln
85 90 95
Gln Ser Thr Glu Ser Leu Thr Leu Asn Pro Ala Ala Ser Val Ser Pro
100 105 110
Ser Glu Thr Glu Pro Ala Ser Thr Pro Asp Thr Thr Asn Arg Leu Ser
115 120 125
Ser Val Asp Arg Ser Thr Thr Gln Pro Ser Glu Ser Arg Thr Lys Thr
130 135 140
Lys Leu Thr Val His Lys Lys Asn Ile Pro Ser Thr Val Ser Arg Thr
145 150 155 160
Gln Ser Ser Ile Arg Ala Thr Thr Lys Ala Val Leu Arg Ala Thr Ala
165 170 175
Phe Arg Thr Ser Ser Thr Gly Glu Arg Pro Thr Thr Ser Val Gln
180 185 190
Ser Asp Ser Ser Thr Thr Thr Gln Asn His Glu Glu Thr Gly Ser Ala
195 200 205
Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Asn Xaa His Thr Asn Ile
210 215 220
Val Lys Pro Asn
225

<210> 146
<211> 228
<212> PRT
<213> Human metapneumovirus

<220>
<221> VARIANT
<222> 220
<223> Xaa = unknown amino acid or other

<400> 146
Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala
1 5 10 15
Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
20 25 30
Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
35 40 45
Leu Ile Ile Asn Tyr Thr Ile Gln Lys Thr Ser Glu Ser Glu His
50 55 60
His Thr Ser Ser Pro Pro Thr Glu Ser Asn Lys Glu Thr Ser Thr Ile

65	70	75	80
Ser Ile Asp Asn Pro Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln			
85	90	95	
Gln Ser Thr Glu Ser Leu Thr Leu Ser Pro Thr Ala Ser Val Ser Pro			
100	105	110	
Ser Glu Thr Glu Pro Ala Ser Thr Ser Asp Thr Thr Ser Arg Leu Ser			
115	120	125	
Ser Val Asp Arg Ser Thr Thr Gln Pro Ser Glu Ser Arg Ala Arg Thr			
130	135	140	
Lys Pro Thr Val His Lys Asn Ile Pro Ser Thr Val Ser Arg Thr			
145	150	155	160
Gln Ser Pro Leu Arg Ala Thr Thr Lys Ala Val Leu Arg Ala Thr Ala			
165	170	175	
Phe Arg Thr Ser Ser Thr Gly Glu Gly Pro Thr Thr Ser Val Gln			
180	185	190	
Ser Asp Ser Ser Thr Thr Thr Gln Asn His Glu Glu Thr Gly Ser Ala			
195	200	205	
Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Asn Xaa His Thr Asn Ile			
210	215	220	
Val Lys Pro Asn			
225			

<210> 147

<211> 228

<212> PRT

<213> Human metapneumovirus

<220>

<221> VARIANT

<222> 220

<223> Xaa = unknown amino acid or other

<400> 147

Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala			
1	5	10	15
Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser			
20	25	30	
Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr			
35	40	45	
Leu Ile Ile Asn Tyr Thr Ile Gln Lys Thr Thr Ser Glu Ser Glu His			
50	55	60	
His Thr Ser Ser Pro Pro Thr Glu Ser Asn Lys Glu Ala Ser Thr Ile			
65	70	75	80
Ser Thr Asp Asn Pro Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln			
85	90	95	
Gln Ser Thr Glu Asn Pro Thr Leu Asn Pro Ala Ala Ser Val Ser Ser			
100	105	110	
Ser Glu Thr Glu Pro Ala Ser Thr Pro Asp Thr Thr Asn Arg Leu Ser			
115	120	125	
Ser Val Asp Arg Ser Thr Ala Gln Pro Ser Glu Ser Arg Thr Lys Thr			
130	135	140	
Lys Pro Thr Val His Thr Arg Asn Asn Pro Ser Thr Ala Ser Ser Thr			
145	150	155	160
Gln Ser Pro Pro Arg Val Thr Thr Lys Ala Ile Leu Arg Ala Thr Val			
165	170	175	
Phe Arg Met Ser Ser Thr Gly Lys Arg Pro Ala Thr Thr Leu Val Gln			
180	185	190	
Ser Asp Ser Ser Thr Thr Thr Gln Asn His Glu Glu Thr Gly Ser Ala			
195	200	205	
Asn Ser Gln Ala Ser Ala Ser Thr Met Gln Asn Xaa His Ser Asn Asn			
210	215	220	

Ile Lys Pro Asn
225

<210> 148
<211> 228
<212> PRT
<213> Human metapneumo virus

<400> 148
Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala
1 5 10 15
Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
20 25 30
Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
35 40 45
Leu Ile Ile Asn Tyr Thr Ile Gln Lys Thr Ser Glu Ser Glu His
50 55 60
His Thr Ser Ser Pro Pro Thr Glu Ser Asn Lys Glu Thr Ser Thr Ile
65 70 75 80
Ser Ile Asp Asn Ser Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln
85 90 95
Gln Ser Thr Glu Ser Leu Thr Leu Ser Pro Thr Ala Ser Val Ser Pro
100 105 110
Ser Glu Thr Glu Pro Ala Ser Thr Ser Asp Thr Thr Asn Arg Leu Ser
115 120 125
Ser Val Asp Arg Ser Thr Thr Gln Pro Ser Glu Ser Arg Ala Arg Thr
130 135 140
Lys Pro Thr Val His Lys Asn Ile Pro Ser Thr Val Ser Arg Thr
145 150 155 160
Gln Ser Pro Leu Arg Ala Thr Thr Lys Ala Val Leu Arg Ala Thr Ala
165 170 175
Phe Arg Met Ser Ser Thr Gly Glu Gly Pro Thr Thr Ser Val Gln
180 185 190
Ser Asp Ser Ser Thr Thr Thr Gln Asn His Glu Glu Thr Gly Ser Ala
195 200 205
Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Asn Gln His Thr Asn Ile
210 215 220
Ala Lys Pro Asn
225

<210> 149
<211> 228
<212> PRT
<213> Human metapneumo virus

<400> 149
Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala
1 5 10 15
Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
20 25 30
Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
35 40 45
Leu Ile Ile Asn Tyr Thr Ile Gln Lys Thr Ser Glu Ser Glu His
50 55 60
His Thr Ser Ser Pro Pro Thr Glu Ser Asn Lys Glu Thr Ser Thr Ile
65 70 75 80
Pro Ile Asp Asn Pro Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln
85 90 95
Gln Ser Thr Glu Ser Leu Thr Leu Tyr Pro Thr Ser Ser Val Ser Ser
100 105 110

Ser Glu Thr Glu Pro Ala Ser Thr Pro Gly Ile Thr Asn His Leu Ser
 115 120 125
 Phe Val Asp Arg Ser Thr Thr Gln Pro Ser Glu Ser Arg Thr Lys Thr
 130 135 140
 Asn Arg Thr Val His Lys Lys Asn Ile Ser Ser Thr Val Ser Arg Thr
 145 150 155 160
 Gln Ser Pro Pro Arg Thr Thr Ala Lys Ala Val Pro Arg Ala Thr Ala
 165 170 175
 Leu Arg Thr Ser Ser Thr Gly Glu Arg Pro Thr Thr Pro Val Gln
 180 185 190
 Pro Asp Ser Ser Thr Thr Gln Asn His Glu Glu Thr Gly Ser Ala
 195 200 205
 Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Asn Gln His Thr Asn Ile
 210 215 220
 Ala Arg Pro Asn
 225

<210> 150
 <211> 228
 <212> PRT
 <213> Human metapneumo virus

<400> 150
 Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala
 1 5 10 15
 Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
 20 25 30
 Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
 35 40 45
 Leu Ile Ile Asn Tyr Thr Ile Gln Lys Thr Thr Ser Glu Ser Glu His
 50 55 60
 His Thr Ser Ser Pro Pro Thr Glu Ser Asn Lys Glu Thr Ser Thr Ile
 65 70 75 80
 Pro Ile Asp Asn Pro Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln
 85 90 95
 Gln Ser Ala Glu Ser Leu Thr Leu Tyr Pro Thr Ser Ser Val Ser Ser
 100 105 110
 Ser Glu Thr Glu Pro Ala Ser Thr Pro Gly Ile Thr Asn His Leu Ser
 115 120 125
 Phe Val Asp Arg Ser Thr Thr Gln Pro Ser Glu Ser Arg Thr Lys Thr
 130 135 140
 Asn Arg Thr Val His Lys Lys Asn Ile Ser Ser Thr Val Ser Arg Thr
 145 150 155 160
 Gln Ser Pro Pro Arg Thr Thr Ala Lys Ala Val Pro Arg Ala Thr Ala
 165 170 175
 Leu Arg Thr Ser Ser Thr Gly Glu Arg Pro Thr Thr Pro Val Gln
 180 185 190
 Pro Asp Ser Ser Thr Thr Gln Asn His Glu Glu Thr Gly Ser Ala
 195 200 205
 Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Asn Gln His Thr Asn Ile
 210 215 220
 Ala Arg Pro Asn
 225

<210> 151
 <211> 228.
 <212> PRT
 <213> Human metapneumo virus

<400> 151

Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala
 1 5 10 15
 Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
 20 25 30
 Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
 35 40 45
 Leu Ile Ile Asn Tyr Thr Ile Gln Lys Thr Thr Ser Glu Ser Glu His
 50 55 60
 His Thr Ser Ser Pro Pro Thr Glu Ser Asn Lys Glu Thr Ser Thr Ile
 65 70 75 80
 Pro Ile Asp Asn Pro Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln
 85 90 95
 Gln Ser Thr Glu Ser Leu Thr Leu Tyr Pro Thr Ser Ser Val Ser Ser
 100 105 110
 Ser Glu Thr Glu Pro Ala Ser Thr Pro Gly Ile Thr Asn His Leu Ser
 115 120 125
 Phe Val Asp Arg Ser Thr Thr Gln Pro Ser Glu Ser Arg Thr Lys Thr
 130 135 140
 Asn Arg Thr Val His Lys Lys Asn Ile Ser Ser Thr Val Ser Arg Thr
 145 150 155 160
 Gln Ser Pro Pro Arg Thr Thr Ala Lys Ala Val Pro Arg Ala Thr Ala
 165 170 175
 Leu Arg Thr Ser Thr Gly Glu Arg Pro Thr Thr Pro Val Gln
 180 185 190
 Pro Asp Ser Ser Thr Thr Gln Asn His Glu Glu Thr Gly Ser Ala
 195 200 205
 Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Asn Gln His Thr Asn Ile
 210 215 220
 Ala Arg Pro Asn
 225

<210> 152
 <211> 228
 <212> PRT
 <213> Human metapneumo virus

<400> 152
 Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala
 1 5 10 15
 Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
 20 25 30
 Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
 35 40 45
 Leu Ile Ile Asn Tyr Thr Ile Gln Gln Thr Thr Ser Glu Ser Glu His
 50 55 60
 His Thr Ser Ser Pro Pro Thr Glu Ser Asn Lys Glu Ala Ser Thr Ile
 65 70 75 80
 Ser Thr Asp Asn Pro Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln
 85 90 95
 Gln Ser Thr Glu Asn Pro Thr Leu Asn Pro Ala Ala Ser Ala Ser Pro
 100 105 110
 Ser Glu Thr Glu Ser Ala Ser Thr Pro Asp Thr Thr Asn Arg Leu Ser
 115 120 125
 Ser Val Asp Arg Ser Thr Val Gln Pro Ser Glu Asn Arg Thr Lys Thr
 130 135 140
 Lys Leu Thr Val His Thr Arg Asn Asn Leu Ser Thr Ala Ser Ser Thr
 145 150 155 160
 Gln Ser Pro Pro Arg Ala Thr Thr Lys Ala Ile Arg Arg Ala Thr Thr
 165 170 175
 Leu Arg Met Ser Ser Thr Gly Arg Arg Pro Thr Thr Thr Leu Val Gln
 180 185 190

Ser Asp Ser Ser Thr Thr Gln Asn His Glu Glu Thr Gly Ser Ala
 195 200 205
 Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Asn Gln His Thr Asn Asn
 210 215 220
 Ile Lys Pro Asn
 225

<210> 153
<211> 228
<212> PRT
<213> Human metapneumo virus

<400> 153
Met Glu Val Lys Val Glu Asn Ile Arg Ala Ile Asp Met Leu Lys Ala
 1 5 10 15
 Arg Val Lys Asn Arg Val Ala Arg Ser Lys Cys Phe Lys Asn Ala Ser
 20 25 30
 Leu Ile Leu Ile Gly Ile Thr Thr Leu Ser Ile Ala Leu Asn Ile Tyr
 35 40 45
 Leu Ile Ile Asn Tyr Thr Ile Gln Lys Thr Thr Ser Glu Ser Glu His
 50 55 60
 His Thr Ser Ser Pro Pro Thr Glu Ser Asn Lys Glu Ala Ser Thr Ile
 65 70 75 80
 Ser Thr Asp Asn Pro Asp Ile Asn Pro Asn Ser Gln His Pro Thr Gln
 85 90 95
 Gln Ser Thr Glu Asn Pro Thr Leu Asn Pro Ala Ala Ser Ala Ser Pro
 100 105 110
 Ser Glu Thr Glu Ser Ala Ser Thr Pro Asp Thr Thr Asn Arg Leu Ser
 115 120 125
 Ser Val Asp Arg Ser Thr Val Gln Pro Ser Glu Asn Arg Thr Lys Thr
 130 135 140
 Lys Leu Thr Val His Thr Arg Asn Asn Leu Ser Thr Ala Ser Ser Thr
 145 150 155 160
 Gln Ser Pro Pro Arg Ala Thr Thr Lys Ala Ile Arg Arg Ala Thr Thr
 165 170 175
 Leu Arg Met Ser Ser Thr Gly Arg Arg Pro Thr Thr Thr Leu Val Gln
 180 185 190
 Ser Asp Ser Ser Thr Thr Gln Asn His Glu Glu Thr Gly Ser Ala
 195 200 205
 Asn Pro Gln Ala Ser Ala Ser Thr Met Gln Asn Gln His Thr Asn Asn
 210 215 220
 Ile Lys Pro Asn
 225

<210> 154
<211> 231
<212> PRT
<213> Human metapneumovirus

<220>
<221> VARIANT
<222> 225
<223> Xaa = unknown amino acid or other

<400> 154
Met Glu Val Arg Val Glu Asn Ile Arg Ala Ile Asp Met Phe Lys Ala
 1 5 10 15
 Lys Ile Lys Asn Arg Ile Arg Ser Ser Arg Cys Tyr Arg Asn Ala Thr
 20 25 30
 Leu Ile Leu Ile Gly Leu Thr Ala Leu Ser Met Ala Leu Asn Ile Phe

35	40	45
Leu Ile Ile Asp His Ala Thr	Leu Arg Asn Met Ile	Lys Thr Glu Asn
50	55	60
Cys Ala Asn Met Pro Ser Ala Glu Pro Ser Lys	Lys Thr Pro Met Thr	
65	70	75
Ser Thr Ala Gly Pro Asn Thr Lys Pro Asn Pro Gln Gln Ala Thr Gln		80
85	90	95
Trp Thr Thr Glu Asn Ser Thr Ser Pro Val Ala Thr Pro Glu Gly His		
100	105	110
Pro Tyr Thr Gly Thr Thr Gln Thr Ser Asp Thr Thr Ala Pro Gln Gln		
115	120	125
Thr Thr Asp Lys His Thr Ala Pro Leu Lys Ser Thr Asn Glu Gln Ile		
130	135	140
Thr Gln Thr Thr Glu Lys Lys Thr Ile Arg Ala Thr Thr Gln Lys		
145	150	155
Arg Glu Lys Gly Lys Glu Asn Thr Asn Gln Thr Thr Ser Thr Ala Ala		160
165	170	175
Thr Gln Thr Thr Asn Thr Asn Gln Ile Arg Asn Ala Ser Glu Thr		
180	185	190
Ile Thr Thr Ser Asp Arg Pro Arg Thr Asp Thr Thr Gln Ser Ser		
195	200	205
Glu Gln Thr Thr Arg Ala Thr Asp Pro Ser Ser Pro Pro His His Ala		
210	215	220
Xaa Arg Gly Ala Lys Leu Lys		
225	230	

<210> 155

<211> 231

<212> PRT

<213> Human metapneumo virus.

<400> 155

Met Glu Val Arg Val Glu Asn Ile Arg Ala Ile Asp Met Phe Lys Ala		
1	5	10
Lys Ile Lys Asn Arg Ile Arg Ser Ser Arg Cys Tyr Arg Asn Ala Thr		15
20	25	30
Leu Ile Leu Ile Gly Leu Thr Ala Leu Ser Met Ala Leu Asn Ile Phe		
35	40	45
Leu Ile Ile Asp His Ala Thr Leu Arg Asn Met Ile Lys Thr Glu Asn		
50	55	60
Cys Ala Asn Met Pro Ser Ala Glu Pro Ser Lys Thr Pro Met Thr		
65	70	75
Ser Thr Ala Gly Pro Ser Thr Glu Pro Asn Pro Gln Gln Ala Thr Gln		80
85	90	95
Trp Thr Thr Glu Asn Ser Thr Ser Pro Ala Ala Thr Leu Glu Ser His		
100	105	110
Pro Tyr Thr Gly Thr Thr Gln Thr Pro Asp Ile Thr Ala Pro Gln Gln		
115	120	125
Thr Thr Asp Lys His Thr Ala Leu Pro Lys Ser Thr Asn Glu Gln Ile		
130	135	140
Thr Gln Thr Thr Glu Lys Lys Thr Arg Ala Thr Thr Gln Lys		
145	150	155
Arg Glu Lys Glu Lys Glu Asn Thr Asn Gln Thr Thr Ser Thr Ala Ala		160
165	170	175
Thr Gln Thr Thr Asn Thr Asn Gln Thr Arg Asn Ala Ser Glu Thr		
180	185	190
Ile Thr Thr Ser Asp Arg Pro Arg Ile Asp Thr Thr Gln Ser Ser		
195	200	205
Asp Gln Thr Thr Arg Ala Thr Asp Pro Ser Ser Pro Pro His His Ala		
210	215	220
Gln Ser Gly Ala Lys Pro Lys		

225

230

<210> 156
<211> 231
<212> PRT
<213> Human metapneumo virus

<400> 156

Met	Glu	Val	Arg	Val	Glu	Asn	Ile	Arg	Ala	Ile	Asp	Met	Phe	Lys	Ala
1					5				10					15	
Lys	Ile	Lys	Asn	Arg	Ile	Arg	Ser	Ser	Arg	Cys	Tyr	Arg	Asn	Ala	Thr
					20			25						30	
Leu	Ile	Leu	Ile	Gly	Leu	Thr	Ala	Leu	Ser	Met	Ala	Leu	Asn	Ile	Phe
					35			40				45			
Leu	Ile	Ile	Asp	His	Ala	Thr	Leu	Arg	Asn	Met	Ile	Lys	Thr	Glu	Asn
					50			55				60			
Cys	Ala	Asn	Met	Pro	Pro	Ala	Glu	Pro	Ser	Lys	Lys	Thr	Pro	Met	Thr
					65			70			75			80	
Ser	Thr	Ala	Gly	Pro	Asn	Thr	Lys	Pro	Asn	Pro	Gln	Gln	Ala	Thr	Gln
					85				90			95			
Trp	Thr	Thr	Glu	Asn	Ser	Thr	Phe	Pro	Ala	Ala	Thr	Ser	Glu	Gly	His
					100			105				110			
Leu	His	Thr	Gly	Thr	Thr	Gln	Thr	Pro	Asp	Thr	Thr	Ala	Pro	Gln	Gln
					115			120				125			
Thr	Thr	Asp	Lys	His	Thr	Ala	Leu	Pro	Lys	Ser	Thr	Asn	Glu	Gln	Ile
					130			135				140			
Thr	Gln	Thr	Thr	Thr	Glu	Lys	Lys	Thr	Thr	Arg	Ala	Thr	Thr	Gln	Arg
					145			150			155			160	
Arg	Glu	Lys	Gly	Lys	Glu	Asn	Thr	Asn	Gln	Thr	Thr	Ser	Thr	Ala	Ala
					165				170				175		
Thr	Gln	Thr	Thr	Asn	Thr	Asn	Gln	Ile	Arg	Asn	Ala	Ser	Glu	Thr	
					180			185				190			
Ile	Thr	Thr	Ser	Asp	Arg	Pro	Arg	Thr	Asp	Ser	Thr	Thr	Gln	Ser	Ser
					195			200				205			
Glu	Gln	Thr	Thr	Arg	Ala	Thr	Asp	Pro	Ser	Ser	Pro	Pro	His	His	Ala
					210			215			220				
Gln	Gly	Ser	Ala	Lys	Pro	Lys									
					225			230							

<210> 157
<211> 231
<212> PRT
<213> Human metapneumo virus

<400> 157

Met	Glu	Val	Arg	Val	Glu	Asn	Ile	Arg	Ala	Ile	Asp	Met	Phe	Lys	Ala
1					5				10					15	
Lys	Ile	Lys	Asn	Arg	Ile	Arg	Ser	Ser	Arg	Cys	Tyr	Arg	Asn	Ala	Thr
					20			25				30			
Leu	Ile	Leu	Ile	Gly	Leu	Thr	Ala	Leu	Ser	Met	Ala	Leu	Asn	Ile	Phe
					35			40				45			
Leu	Ile	Ile	Asp	His	Ala	Thr	Leu	Arg	Asn	Met	Ile	Lys	Thr	Glu	Asn
					50			55				60			
Cys	Ala	Asn	Met	Pro	Pro	Ala	Glu	Pro	Ser	Arg	Lys	Thr	Pro	Met	Thr
					65			70			75			80	
Ser	Thr	Ala	Gly	Pro	Asn	Thr	Lys	Pro	Asn	Pro	Gln	Gln	Ala	Thr	Gln
					85				90			95			
Trp	Thr	Thr	Glu	Asn	Ser	Thr	Ser	Pro	Ala	Ala	Thr	Pro	Glu	Gly	His
					100			105				110			
Leu	His	Thr	Gly	Thr	Thr	Gln	Thr	Pro	Asp	Thr	Ala	Pro	Gln	Gln	

115	120	125													
Thr	Thr	Asp	Lys	His	Thr	Ala	Leu	Pro	Lys	Ser	Thr	Asn	Glu	Gln	Ile
130						135					140				
Thr	Gln	Ala	Thr	Thr	Glu	Lys	Lys	Thr	Thr	Arg	Glu	Thr	Thr	Gln	Arg
145						150				155					160
Arg	Glu	Lys	Gly	Lys	Glu	Asn	Thr	Asn	Gln	Thr	Thr	Ser	Thr	Ala	Ala
						165				170					175
Thr	Gln	Thr	Thr	Asn	Thr	Thr	Asn	Gln	Ile	Arg	Asn	Ala	Ser	Glu	Thr
						180				185					190
Ile	Thr	Thr	Ser	Asp	Arg	Pro	Arg	Thr	Asp	Ser	Thr	Thr	Gln	Ser	Ser
						195				200					205
Glu	Gln	Thr	Thr	Gln	Ala	Thr	Asp	Pro	Ser	Ser	Pro	Ala	His	His	Ala
						210				215					220
Gln	Gly	Ser	Ala	Lys	Pro	Lys									
						225				230					

<210> 158

<211> 231

<212> PRT

<213> Human metapneumo virus

<400> 158

Met	Glu	Val	Arg	Val	Glu	Asn	Ile	Arg	Ala	Ile	Asp	Met	Phe	Lys	Ala
1							5			10					15
Lys	Ile	Lys	Asn	Arg	Ile	Arg	Ser	Ser	Arg	Cys	Tyr	Arg	Asn	Ala	Thr
							20			25					30
Leu	Ile	Leu	Ile	Gly	Leu	Thr	Ala	Leu	Ser	Met	Ala	Leu	Asn	Ile	Phe
							35			40					45
Leu	Ile	Ile	Asp	His	Ala	Thr	Leu	Arg	Asn	Met	Ile	Lys	Thr	Glu	Asn
							50			55					60
Cys	Ala	Asn	Met	Pro	Pro	Ala	Glu	Pro	Ser	Lys	Lys	Thr	Pro	Met	Thr
							65			70					80
Ser	Thr	Ala	Gly	Leu	Asn	Thr	Lys	Pro	Asn	Pro	Gln	Gln	Ala	Thr	Gln
							85			90					95
Trp	Thr	Thr	Glu	Asn	Ser	Thr	Ser	Pro	Ala	Ala	Thr	Pro	Glu	Gly	His
							100			105					110
Leu	His	Thr	Gly	Thr	Thr	Gln	Thr	Pro	Asp	Thr	Thr	Ala	Pro	Gln	Gln
							115			120					125
Thr	Thr	Asp	Lys	His	Thr	Ala	Leu	Pro	Lys	Ser	Thr	Asn	Glu	Gln	Ile
							130			135					140
Thr	Gln	Thr	Thr	Thr	Glu	Lys	Lys	Thr	Arg	Ala	Thr	Thr	Gln	Arg	
							145			150					160
Arg	Glu	Lys	Gly	Lys	Glu	Asn	Thr	Asn	Gln	Thr	Thr	Ser	Thr	Ala	Ala
							165			170					175
Thr	Gln	Thr	Thr	Asn	Thr	Asn	Gln	Ile	Arg	Asn	Ala	Ser	Glu	Thr	
							180			185					190
Ile	Thr	Thr	Ser	Asp	Arg	Pro	Arg	Thr	Asp	Ser	Thr	Thr	Gln	Ser	Ser
							195			200					205
Glu	Gln	Thr	Thr	Arg	Ala	Thr	Asp	Pro	Ser	Ser	Pro	Pro	His	His	Ala
							210			215					220
Gln	Gly	Ser	Ala	Lys	Pro	Lys									
							225			230					

<210> 159

<211> 231

<212> PRT

<213> Human metapneumo virus

<400> 159

Met Glu Val Arg Val Glu Asn Ile Arg Ala Ile Asp Met Phe Lys Ala

1	5	10	15
Lys Ile Lys Asn Arg Ile Arg Ser Ser Arg Cys Tyr Arg Asn Ala Thr			
20	25	30	
Leu Ile Leu Ile Gly Leu Thr Ala Leu Ser Met Ala Leu Asn Ile Phe			
35	40	45	
Leu Ile Ile Asp His Ala Thr Leu Arg Asn Met Ile Lys Thr Glu Asn			
50	55	60	
Cys Ala Asn Met Pro Pro Ala Glu Pro Ser Lys Lys Thr Pro Met Thr			
65	70	75	80
Ser Thr Ala Gly Pro Asn Thr Lys Pro Asn Pro Gln Gln Ala Thr Gln			
85	90	95	
Trp Thr Thr Glu Asn Ser Thr Ser Pro Ala Ala Thr Pro Glu Gly His			
100	105	110	
Leu His Thr Gly Thr Thr Gln Thr Pro Asp Thr Thr Ala Pro Gln Gln			
115	120	125	
Thr Thr Asp Lys His Thr Ala Leu Pro Lys Ser Thr Asn Glu Gln Ile			
130	135	140	
Thr Gln Thr Thr Glu Lys Lys Thr Thr Arg Ala Thr Thr Gln Arg			
145	150	155	160
Arg Glu Lys Gly Lys Glu Asn Thr Asn Gln Thr Thr Ser Thr Ala Ala			
165	170	175	
Thr Gln Thr Thr Asn Thr Thr Asn Gln Ile Arg Asn Ala Ile Glu Thr			
180	185	190	
Ile Thr Thr Ser Asp Arg Pro Arg Thr Asp Ser Thr Thr Gln Ser Ser			
195	200	205	
Glu Gln Thr Thr Arg Ala Thr Asp Pro Ser Ser His Pro His His Ala			
210	215	220	
Gln Gly Ser Ala Lys Pro Lys			
225	230		

<210> 160

<211> 236

<212> PRT

<213> Human metapneumo virus

<400> 160

Met Glu Val Arg Val Glu Asn Ile Arg Ala Ile Asp Met Phe Lys Ala			
1	5	10	15
Lys Met Lys Asn Arg Ile Arg Ser Ser Lys Cys Tyr Arg Asn Ala Thr			
20	25	30	
Leu Ile Leu Ile Gly Leu Thr Ala Leu Ser Met Ala Leu Asn Ile Phe			
35	40	45	
Leu Ile Ile Asp Tyr Ala Met Leu Lys Asn Met Thr Lys Val Glu His			
50	55	60	
Cys Val Asn Met Pro Pro Val Glu Pro Ser Lys Lys Thr Pro Met Thr			
65	70	75	80
Ser Ala Val Asp Leu Asn Thr Lys Pro Asn Pro Gln Gln Ala Thr Gln			
85	90	95	
Leu Ala Ala Glu Asp Ser Thr Ser Leu Ala Ala Thr Ser Glu Asp His			
100	105	110	
Leu His Thr Gly Thr Thr Pro Thr Pro Asp Ala Thr Val Ser Gln Gln			
115	120	125	
Thr Thr Asp Glu Tyr Thr Thr Leu Leu Arg Ser Thr Asn Arg Gln Thr			
130	135	140	
Thr Gln Thr Thr Glu Lys Lys Pro Thr Gly Ala Thr Thr Lys Lys			
145	150	155	160
Glu Thr Thr Thr Arg Thr Thr Ser Thr Ala Ala Thr Gln Thr Leu Asn			
165	170	175	
Thr Thr Asn Gln Thr Ser Tyr Val Arg Glu Ala Thr Thr Thr Ser Ala			
180	185	190	
Arg Ser Arg Asn Ser Ala Thr Thr Gln Ser Ser Asp Gln Thr Thr Gln			

195	200	205
Ala Ala Asp Pro Ser Ser Gln Pro His His Thr Gln	Lys Ser Thr Thr	
210	215	220
Thr Thr Tyr Asn Thr Asp Thr Ser Ser Pro Ser Ser		
225	230	235

<210> 161
<211> 236
<212> PRT
<213> Human metapneumovirus

<220>
<221> VARIANT
<222> 220, 227
<223> Xaa = unknown amino acid or other

<400> 161

Met	Glu	Val	Arg	Val	Glu	Asn	Ile	Arg	Thr	Ile	Asp	Met	Phe	Lys	Ala	
1					5				10				15			
Lys	Met	Lys	Asn	Arg	Ile	Arg	Ser	Ser	Lys	Cys	Tyr	Arg	Asn	Ala	Thr	
					20			25				30				
Leu	Ile	Leu	Ile	Gly	Leu	Thr	Ala	Leu	Ser	Met	Ala	Leu	Asn	Ile	Phe	
					35			40				45				
Leu	Ile	Ile	Asp	Tyr	Ala	Thr	Phe	Lys	Asn	Met	Thr	Lys	Val	Glu	His	
					50			55				60				
Cys	Ala	Asn	Met	Pro	Pro	Val	Glu	Pro	Ser	Lys	Lys	Thr	Pro	Met	Thr	
					65			70			75			80		
Ser	Thr	Val	Asp	Ser	Ser	Thr	Gly	Pro	Asn	Pro	Gln	Gln	Thr	Thr	Gln	
					85			90				95				
Trp	Thr	Thr	Glu	Asp	Ser	Thr	Ser	Leu	Ala	Ala	Thr	Ser	Glu	Asp	His	
					100			105				110				
Leu	His	Thr	Gly	Thr	Thr	Pro	Thr	Leu	Asp	Ala	Thr	Val	Ser	Gln	Gln	
					115			120				125				
Thr	Pro	Asp	Lys	His	Thr	Thr	Pro	Leu	Arg	Ser	Thr	Asn	Gly	Gln	Thr	
					130			135				140				
Thr	Gln	Thr	Thr	Thr	Glu	Lys	Lys	Pro	Thr	Arg	Ala	Ile	Ala	Lys	Lys	
					145			150			155			160		
Glu	Thr	Thr	Asn	Gln	Thr	Thr	Ser	Thr	Ala	Ala	Thr	Gln	Thr	Phe	Asn	
					165			170				175				
Thr	Thr	Asn	Gln	Thr	Arg	Asn	Gly	Arg	Glu	Thr	Thr	Ile	Thr	Ser	Ala	
					180			185				190				
Arg	Ser	Arg	Asn	Asn	Asp	Ala	Thr	Thr	Gln	Ser	Ser	Glu	Gln	Thr	Asn	Gln
					195			200				205				
Thr	Thr	Asp	Pro	Ser	Ser	Gln	Pro	His	His	Ala	Xaa	Ile	Ser	Thr	Ile	
					210			215				220				
Thr	Ile	Xaa	Thr	Gln	His	Arg	His	Ile	Phe	Ser	Lys					
					225			230			235					

<210> 162
<211> 236
<212> PRT
<213> Human metapneumovirus

<220>
<221> VARIANT
<222> 208
<223> Xaa = unknown amino acid or other

<400> 162
Met Glu Val Arg Val Glu Asn Ile Arg Ala Ile Asp Met Phe Lys Ala

1	5	10	15
Lys Met Lys Asn Arg Ile Arg Ser Ser	Lys Cys Tyr Arg Asn Ala Thr		
20	25	30	
Leu Ile Leu Ile Gly Leu Thr Ala Leu Ser Met Ala Leu Asn Ile Phe			
35	40	45	
Leu Ile Ile Asp Tyr Ala Met Leu Lys Asn Met Thr Lys Val Glu His			
50	55	60	
Cys Val Asn Met Pro Pro Val Glu Pro Ser Lys Lys Thr Pro Met Thr			
65	70	75	80
Ser Ala Val Asp Leu Asn Thr Lys Leu Asn Pro Gln Gln Ala Thr Gln			
85	90	95	
Leu Thr Thr Glu Asp Ser Thr Ser Leu Ala Ala Thr Ser Glu Asp His			
100	105	110	
Leu Leu Thr Gly Thr Thr Pro Thr Pro Asp Ala Thr Val Ser Gln Gln			
115	120	125	
Thr Thr Asp Glu His Thr Thr Leu Leu Arg Ser Thr Asn Arg Gln Thr			
130	135	140	
Thr Gln Thr Thr Glu Lys Lys Pro Thr Gly Ala Thr Thr Lys Lys			
145	150	155	160
Glu Thr Thr Arg Thr Thr Ser Thr Ala Ala Thr Gln Thr Leu Asn			
165	170	175	
Thr Thr Asn Gln Thr Ser Asn Gly Arg Glu Ala Thr Thr Thr Ser Thr			
180	185	190	
Arg Ser Arg Asn Gly Ala Thr Thr Gln Asn Ser Asp Gln Thr Thr Xaa			
195	200	205	
Thr Ala Asp Pro Ser Ser Gln Pro His His Thr Gln Lys Ser Thr Thr			
210	215	220	
Thr Thr Tyr Asn Thr Asp Thr Ser Ser Pro Ser Ser			
225	230	235	

<210> 163

<211> 236

<212> PRT

<213> Human metapneumo virus

<400> 163

Met Glu Val Arg Val Glu Asn Ile Arg Ala Ile Asp Met Phe Lys Ala			
1	5	10	15
Lys Met Lys Asn Arg Ile Arg Ser Ser Lys Cys Tyr Arg Asn Ala Thr			
20	25	30	
Leu Ile Leu Ile Gly Leu Thr Ala Leu Ser Met Ala Leu Asn Ile Phe			
35	40	45	
Leu Ile Ile Asp Tyr Ala Thr Leu Lys Asn Met Thr Lys Val Glu His			
50	55	60	
Cys Val Asn Met Pro Pro Val Glu Pro Ser Lys Lys Thr Pro Met Thr			
65	70	75	80
Ser Ala Val Asp Leu Asn Thr Lys Leu Asn Pro Gln Gln Ala Thr Gln			
85	90	95	
Leu Thr Thr Glu Asp Ser Thr Ser Leu Ala Ala Thr Ser Glu Gly His			
100	105	110	
Pro His Thr Gly Thr Thr Pro Thr Pro Asp Ala Thr Val Ser Gln Gln			
115	120	125	
Thr Thr Asp Glu His Thr Thr Leu Leu Arg Ser Thr Asn Arg Gln Thr			
130	135	140	
Thr Gln Thr Ala Thr Glu Lys Lys Pro Thr Gly Ala Thr Thr Lys Lys			
145	150	155	160
Glu Thr Thr Arg Thr Thr Ser Thr Ala Ala Thr Gln Thr Pro Asn			
165	170	175	
Thr Thr Asn Gln Thr Ser Asn Gly Arg Glu Ala Thr Thr Ser Ala			
180	185	190	
Arg Ser Arg Asn Gly Ala Thr Thr Gln Asn Ser Asp Gln Ile Thr Gln			

195	200	205
Ala Ala Asp Ser Ser Ser Gln Pro His His Thr Gln Lys Ser Thr Thr		
210	215	220
Thr Ala Tyr Asn Thr Asp Thr Ser Phe Pro Ser Ser		
225	230	235

<210> 164
<211> 236
<212> PRT
<213> Human metapneumo virus

<400> 164

Met Glu Val Arg Val Glu Asn Ile Arg Ala Ile Asp Met Phe Lys Ala			
1	5	10	15
Lys Met Lys Asn Arg Ile Arg Ser Ser Lys Cys Tyr Arg Asn Ala Thr			
20	25	30	
Leu Ile Leu Ile Gly Leu Thr Ala Leu Ser Met Ala Leu Asn Ile Phe			
35	40	45	
Leu Ile Ile Asp Tyr Ala Thr Leu Lys Asn Met Thr Lys Val Glu His			
50	55	60	
Cys Val Asn Met Pro Pro Val Glu Pro Ser Lys Lys Thr Pro Met Thr			
65	70	75	80
Ser Ala Val Asp Ser Asn Thr Lys Pro Asn Pro Gln Gln Ala Thr Gln			
85	90	95	
Leu Thr Thr Glu Asp Ser Thr Ser Leu Ala Ala Thr Leu Glu Asp His			
100	105	110	
Pro His Thr Gly Thr Thr Pro Thr Pro Asp Ala Thr Val Ser Gln Gln			
115	120	125	
Thr Thr Asp Glu His Thr Thr Leu Leu Arg Ser Thr Asn Arg Gln Thr			
130	135	140	
Thr Gln Thr Thr Ala Glu Lys Lys Pro Thr Arg Ala Thr Thr Lys Lys			
145	150	155	160
Glu Thr Thr Thr Arg Thr Thr Ser Thr Ala Ala Thr Gln Thr Leu Asn			
165	170	175	
Thr Thr Asn Gln Thr Ser Asn Gly Arg Glu Ala Thr Thr Ser Ala			
180	185	190	
Arg Ser Arg Asn Asn Ala Thr Thr Gln Ser Ser Asp Gln Thr Thr Gln			
195	200	205	
Ala Ala Glu Pro Ser Ser Gln Ser Gln His Thr Gln Lys Ser Thr Thr			
210	215	220	
Thr Thr Tyr Asn Thr Asp Thr Ser Ser Leu Ser Ser			
225	230	235	

<210> 165
<211> 236
<212> PRT
<213> Human metapneumo virus

<400> 165

Met Glu Val Arg Val Glu Asn Ile Arg Ala Ile Asp Met Phe Lys Ala			
1	5	10	15
Lys Met Lys Asn Arg Ile Arg Ser Ser Lys Cys Tyr Arg Asn Ala Thr			
20	25	30	
Leu Ile Leu Ile Gly Leu Ser Ala Leu Ser Met Ala Leu Asn Ile Phe			
35	40	45	
Leu Ile Ile Asp Tyr Ala Lys Ser Lys Asn Met Thr Arg Val Glu His			
50	55	60	
Cys Val Asn Met Pro Pro Val Glu Pro Ser Lys Lys Thr Pro Met Thr			
65	70	75	80
Ser Ala Val Asp Leu Asn Thr Lys Pro Asn Pro Gln Arg Ala Thr Gln			

85	90	95
Leu Thr Thr Glu Asp Ser Thr Ser	Leu Ala Ala Thr Leu	Glu Gly His
100	105	110
Leu His Thr Gly Thr Thr Pro Thr Pro Asp Val	Thr Val Ser Gln Gln	
115	120	125
Thr Thr Asp Glu His Thr Thr Leu Leu Arg Ser	Thr Asn Arg Gln Thr	
130	135	140
Thr Gln Thr Ala Ala Glu Lys Lys Pro Thr Arg	Val Thr Thr Asn Lys	
145	150	155
Glu Thr Ile Thr Arg Thr Ser Thr Ala Ala Thr	Gln Thr Leu Asn	
165	170	175
Thr Thr Asn Gln Thr Asn Asn Gly Arg Glu Ala	Thr Thr Ser Ala	
180	185	190
Arg Ser Arg Asn Asn Ala Thr Thr Gln Ser Ser Asp	Gln Thr Thr Gln	
195	200	205
Ala Ala Asp Pro Ser Ser Gln Ser Gln His Thr	Gln Lys Ser Ile Thr	
210	215	220
Thr Thr Tyr Asn Thr Asp Thr Ser Ser Pro Ser Ser		
225	230	235

<210> 166

<211> 236

<212> PRT

<213> Human metapneumo virus

<400> 166

Met Glu Val Arg Val Glu Asn Ile Arg Ala Ile Asp Met	Phe Lys Ala		
1	5	10	15
Lys Met Lys Asn Arg Ile Arg Ser Ser Lys Cys Tyr Arg	Asn Ala Thr		
20	25	30	
Leu Ile Leu Ile Gly Leu Ser Ala Leu Ser Met Ala	Leu Asn Ile Phe		
35	40	45	
Leu Ile Ile Asp Tyr Ala Lys Ser Lys Thr Met	Thr Arg Val Glu His		
50	55	60	
Cys Val Asn Met Pro Pro Val Glu Pro Ser Lys Lys	Thr Pro Met Thr		
65	70	75	80
Ser Ala Val Asp Leu Asn Thr Lys Pro Asn Pro Gln Gln	Ala Thr Gln		
85	90	95	
Leu Thr Thr Glu Asp Ser Thr Ser Pro Ala Ala Thr	Leu Glu Gly His		
100	105	110	
Leu His Thr Gly Thr Thr Pro Thr Pro Asp Ala Thr	Val Ser Gln Gln		
115	120	125	
Thr Thr Asp Glu His Thr Thr Leu Leu Arg Ser	Thr Asn Arg Gln Thr		
130	135	140	
Thr Gln Thr Thr Ala Glu Lys Lys Pro Thr Arg	Ala Thr Thr Lys Lys		
145	150	155	160
Glu Thr Ile Thr Arg Thr Thr Ser Thr Ala Ala Thr	Gln Thr Leu Asn		
165	170	175	
Thr Thr Asn Gln Thr Ser Asn Gly Arg Glu Ala Thr	Thr Ser Ala		
180	185	190	
Arg Ser Arg Asn Asn Ala Thr Thr Gln Ser Ser Asp	Gln Thr Thr Gln		
195	200	205	
Ala Ala Asp Pro Ser Ser Gln Ser Gln His Thr	Lys Lys Ser Thr Thr		
210	215	220	
Thr Thr Tyr Asn Thr Asp Thr Ser Ser Pro Ser Ser			
225	230	235	

<210> 167

<211> 236

<212> PRT

<213> Human metapneumo virus

<400> 167

Met	Glu	Val	Arg	Val	Glu	Asn	Ile	Arg	Ala	Ile	Asp	Met	Phe	Lys	Ala
1							5			10					15
Lys	Met	Lys	Asn	Arg	Ile	Arg	Ser	Ser	Lys	Cys	Tyr	Arg	Asn	Ala	Thr
					20			25							30
Leu	Ile	Leu	Ile	Gly	Leu	Thr	Ala	Leu	Ser	Met	Ala	Leu	Asn	Ile	Phe
					35			40							45
Leu	Ile	Ile	Asp	Tyr	Ala	Thr	Leu	Lys	Asn	Met	Thr	Lys	Val	Glu	His
					50			55							60
Cys	Val	Asn	Met	Pro	Pro	Val	Glu	Pro	Ser	Lys	Lys	Thr	Pro	Met	Thr
					65			70							80
Ser	Ala	Val	Asp	Leu	Asn	Thr	Lys	Pro	Asn	Pro	Gln	Gln	Ala	Thr	Gln
					85			90							95
Leu	Thr	Thr	Glu	Asp	Ser	Thr	Ser	Leu	Ala	Ala	Thr	Leu	Glu	Asp	His
					100			105							110
Pro	His	Thr	Gly	Thr	Thr	Pro	Thr	Pro	Asp	Ala	Thr	Val	Ser	Gln	Gln
					115			120							125
Thr	Thr	Asp	Glu	His	Thr	Thr	Leu	Leu	Arg	Ser	Thr	Asn	Arg	Gln	Thr
					130			135							140
Thr	Gln	Thr	Thr	Ala	Glu	Lys	Lys	Pro	Thr	Arg	Ala	Thr	Thr	Lys	Lys
					145			150							160
Glu	Thr	Thr	Thr	Arg	Thr	Thr	Ser	Thr	Ala	Ala	Thr	Gln	Thr	Leu	Asn
					165			170							175
Thr	Thr	Asn	Gln	Thr	Ser	Asn	Gly	Arg	Glu	Ala	Thr	Thr	Thr	Ser	Ala
					180			185							190
Arg	Ser	Arg	Asn	Asn	Ala	Thr	Thr	Gln	Ser	Ser	Asp	Gln	Thr	Thr	Gln
					195			200							205
Ala	Ala	Glu	Pro	Asn	Ser	Gln	Ser	Gln	His	Thr	Gln	Lys	Ser	Thr	Thr
					210			215							220
Thr	Thr	Tyr	Asn	Thr	Asp	Thr	Ser	Ser	Leu	Ser	Ser				
					225			230							235

<210> 168

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 168

ataggagttt	acggaagctc	cgtaatttac	atggtgcaac	tgccaatctt	tggggttata	60
gacacgcctt	gctggatagt	aaaagcagcc	ccttcttgcgt	cagaaaaaaaa	ggaaaactat	120
gcttccttct	taagagaaga	ccaaggatgg	tattgtcaaa	atgcagggtc	aactgtttac	180
tacccaaatg	aaaaagactg	tgaaacaaga	ggagaccatg	tcttttgcga	cacagcagca	240
ggaatcaatg	ttgctgagca	gtcaaaggag	tgcacacataa	acatatctac	tactaattac	300
ccatgcaaag	ttagcacagg	aagacatcct	atcgttatgg	ttgcactatc	tcctcttggg	360
gttttgttgc	cttgcataaa	gggagtggc	tgttccatttgc	gcagcaacag	agtagggatc	420
atcaagcaac	tgaacaaagg	ctgcttcttca				449

<210> 169

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 169

ataggagttt	acggaagctc	cgtaatttac	atggtgcaac	tgccaatctt	tggggttata	60
gacacgcctt	gctggatagt	aaaagcagcc	ccttcttgcgt	cagaaaaaaaa	ggaaaactat	120
gcttccttct	taagagaaga	tcaaggatgg	tattgtcaga	atgcagggtc	aactgtttac	180
tacccaaatg	aaaaagactg	cgaaacaaga	ggagaccatg	tcttttgcga	cacagcagca	240
ggaatcaatg	ttgctgagca	gtcaaaggag	tgcacacataa	acatatccac	tactaattac	300
ccatgcaaag	ttagcacagg	aagacatcct	atcgttatgg	ttgcactatc	tcctcttggg	360

gctttggttg cttgtacaa gggagtgagc tggccatttgcagcaacatggatc 420
 atcaagcaac tgaacaaagg ctgcttta 449

<210> 170
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 170
 ataggagtt acggaagctc cgtaatttac atggtgcaac tgccaatctt tggggttata 60
 gacacgcctt gctggatgt aaaagcagcc cttcttgcgt cagaaaaaaaaa ggaaaactat 120
 gcttcctt taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagattg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag tttagcacagg aagacatctt atcagtatgg ttgcactgtc tcctcttggg 360
 gctttggttg cttgtacaa gggagtgagc tggccatttgcagcaacatggatc 420
 atcaagcaac tgaacaaagg ctgcttta 449

<210> 171
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 171
 ataggagtt acggaagctc cgtaatttac atggtgcaac tgccaatctt tggggttata 60
 gacacgcctt gctggatgt aaaagcagcc cttcttgcgt cagaaaaaaaaa ggaaaactat 120
 gcttcctt taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag tttagcacagg aagacatctt atcagtatgg ttgcactgtc tcctcttggg 360
 gctttggttg cttgtacaa gggagtgagc tggccatttgcagcaacatggatc 420
 atcaagcaac tgaacaaagg ctgcttta 449

<210> 172
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 172
 ataggagtt acggaagctc cgtaatttac atggtgcaac tgccaatctt tggggttata 60
 gacacgcctt gctggatgt aaaagcagcc cttcttgcgt cagaaaaaaaaa ggaaaactat 120
 gcttcctt taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagattg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag tttagcacagg aagacatctt atcagtatgg ttgcactgtc tcctcttggg 360
 gctttggttg cttgtacaa gggagtgagc tggccatttgcagcaacatggatc 420
 atcaagcaac tgaacaaagg ctgcttta 449

<210> 173
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 173
 ataggagtt acggaagctc cgtaatttac atggtgcaac tgccaatctt tggggttata 60
 gacacgcctt gctggatgt aaaagcagcc cttcttgcgt cagaaaaaaaaa ggaaaactat 120
 gcttcctt taagagaaga ccaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg tgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag tttagcacagg aagacatctt atcagtatgg ttgcactgtc tcctcttggg 360
 gctttggttg cttgtacaa gggagtgagc tggccatttgcagcaacatggatc 420
 atcaagcaac tgaacaaagg ctgcttta 449

<210> 174
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 174
ataggagttt acggaagctc cgtaattttac atggtgcaac tgccaatctt tggggttata 60
gacacgcctt gctggatagt aaaagcagcc ccttcttgcgtt cagaaaaaaaaa gggaaactat 120
gcttcctct taagagaaga ccaaggatgg tattgtcaga atgcagggtc aactgtttac 180
tacccaaatg aaaaagactg tgaaacaaga ggagaccatg tctttgcga cacagcagca 240
ggaatcaatg ttgctgagca gtcaaaggag tgcaacataa acatatctac tactaattac 300
ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactgtc tcctcttggg 360
gcttgggtg ctgtacaa gggagtgagc tggccatttgcga acagcaacag agtagggatc 420
atcaagcaac tgaacaaagg ctgctctta 449

<210> 175
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 175
ataggagttt acggaagctc cgtaattttac atggtgcaac tgccaatctt tggggttata 60
gacacgcctt gctggatagt aaaagcagcc ccttcttgcgtt cagaaaaaaaaa gggaaactat 120
gcttcctct taagagaaga ccaaggatgg tattgtcaga atgcagggtc aactgtttac 180
tacccaaatg aaaaagactg tgaaacaaga ggagaccatg tctttgcga cacagcagca 240
ggaatcaatg ttgctgagca gtcaaaggag tgcaacataa acatatctac tactaattac 300
ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactgtc tcctcttggg 360
gcttgggtg ctgtacaa gggagtgagc tggccatttgcga acagcaacag agtagggatc 420
atcaagcaac tgaacaaagg ctgctctta 449

<210> 176
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 176
ataggagttt acggaagctc cgtaattttac atggtgcaac tgccaatctt tggggttata 60
gacacgcctt gctggatagt aaaagcagcc ccttcttgcgtt cagaaaaaaaaa gggaaactat 120
gcttcctct taagagaaga tcagggatgg tattgtcaga atgcagggtc aactgtttac 180
tacccaaatg aaaaagactg tgaaacaaga ggagaccatg tctttgcga cacagcagca 240
ggaatcaatg ttgctgagca gtcaaaggag tgcaacataa acatatccac tactaattac 300
ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactgtc tcctcttggg 360
gcttgggtg ctgtacaa gggagtgagc tggccatttgcga acagcaacag agtaggaatc 420
atcaagcaac tgaacaaagg ctgctctta 449

<210> 177
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 177
ataggagttt acggaagctc cgtaattttac atggtgcaac tgccaatctt tggagttata 60
gacacgcctt gctggatagt aaaagcagcc ccttcttgcgtt cagaaaaaaaaa gggaaactat 120
gcttcctct taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
ggaatcaatg ttgctgagca gtcaaaggag tgcaacataa acatatccac tactaattac 300
ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactgtc tcctcttggg 360
gcttgggtg ctgtacaa gggagtgagc tggccatttgcga acagcaacag agtagggatc 420
atcaagcaac tgaacaaagg ctgctctta 449

<210> 178
<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 178

ataggagttt acggaagctc cgtaatttac atggtgcaac tgccaatctt tggggttata 60
 gacacgcctt gttggatagt aaaagcagcc ccttcttgct cagaaaaaaaa gggaaactat 120
 gcttcctct taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag ttagcacagg aagacatctt atcagtatgg ttgcactgtc tcctcttggg 360
 gctttgggtg cttgctacaa gggagtgagc tggccattt gcagcaacag agtagggatc 420
 atcaagcaac tgaacaaagg ctgctctta 449

<210> 179

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 179

ataggagttt acggaagctc cgtaatttac atggtgcaac tgccaatctt tggagttata 60
 gacacgcctt gctggatagt aaaagcgccc ccttcttgct cagaaaaaaaa gggaaactat 120
 gcttcctct taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag ttagcacagg aagacatctt atcagtatgg ttgcactgtc tcctcttggg 360
 gctttgggtg cttgctacaa gggagtgagc tggccattt gcagcaacag agtagggatc 420
 atcaagcaac tgaacaaagg ctgctctta 449

<210> 180

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 180

ataggagttt acggaagctc cgtaatttac atggtgcaac tgccaatctt tggggttata 60
 gacacgcctt gctggatagt aaaagcagcc ccttcttgct cagaaaaaaaa gggaaactat 120
 gcttcctct taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca atatatccac tactaattac 300
 ccatgcaaag ttagcacagg aagacatctt atcagtatgg ttgcactgtc tcctcttggg 360
 gctttgggtg cttgctacaa gggagtgagc tggccattt gcagcaacag agtagggatc 420
 atcaagcaac tgaacaaagg ctgctctta 449

<210> 181

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 181

ataggagttt acggaagctc cgtaatttac atggtgcaac tgccaatctt tggagttata 60
 gacacgcctt gctggatagt aaaagcgccc ccttcttgct cggaaaaaaaa gggaaactat 120
 gcttcctct taagagaaga tcaaagatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag ttagcacagg aagacatctt atcagtatgg ttgcactgtc tcctcttggg 360
 gctttgggtg cttgctacaa gggagtgagc tggccattt gcagcaacag agtagggatc 420
 atcaagcaac tgaacaaagg ctgctctta 449

<210> 182

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 182

ataggagttt atggaagctc cgtaattac atggtgcaac tgccaatctt tggagttata 60
 gacacgcctt gctggatagt aaaagcgccc ccttcttgcgt cagaaaaaaaaa ggaaaactat 120
 gcttcctct taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactgtc tcctcttggg 360
 gcttgggtg cttgtacaa gggagtggc tggccatttgcagcaacag agtagggatc 420
 atcaagcaac tgaacaaagg ctgctctta 449

<210> 183

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 183

ataggagttt atggaagctc cgtaattac atggtgcaac tgccaatctt tggagttata 60
 gacacgcctt gctggatagt aaaagcgccc ccttcttgcgt cagaaaaaaaaa ggaaaactat 120
 gcttcctct taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactgtc tcctcttggg 360
 gcttgggtg cttgtacaa gggagtggc tggccatttgcagcaacag agtagggatc 420
 atcaagcaac tgaacaaagg ctgctctta 449

<210> 184

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 184

ataggagttt acggaagctc cgtaattac atggtgcaac tgccaatctt tggagttata 60
 gacacgcctt gctggatagt aaaagcgccc ccttcttgcgt cagaaaaaaaaa ggaaaactat 120
 gcttcctct taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactgtc tcctcttggg 360
 gcttgggtg cttgtacaa gggagtggc tggccatttgcagcaacag agtagggatc 420
 atcaagcaac tgaacaaagg ctgctctta 449

<210> 185

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 185

ataggagttt atggaagctc cgtaattac atggtgcaac tgccaatctt tggagttata 60
 gacacgcctt gctggatagt aaaagcgccc ccttcttgcgt cagaaaaaaaaa ggaaaactat 120
 gcttcctct taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactgtc tcctcttggg 360
 gcttgggtg cttgtacaa gggagtggc tggccatttgcagcaacag agtagggatc 420
 atcaagcaac tgaacaaagg ctgctctta 449

<210> 186

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 186

ataggagttt atggaagctc cgtaattac atggtgcaac tgccaatctt tggagttata 60

gacacgcctt gctggatagt aaaagcggcc ccttcttgct cagaaaaaaaaa gggaaactat 120
 gcttcctct taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactgtc tcctcttggg 360
 gctttgggtg cttgctacaa gggagtgagc tgccatttgcagcaacag agtagggatc 420
 atcaagcaac tgaacaaagg ctgctctta 449

<210> 187
 <211> 449
 <212> DNA
 <213> Human metapneumo virus .

<400> 187
 ataggagttt atgaaagctc cgtaatttac atggtgcaac tgccaatctt tggagttata 60
 gacacgcctt gctggatagt aaaagcggcc ccttcttgct cagaaaaaaaaa gggaaactat 120
 gcttcctct taagagaaga tcaaggatgg tattgtcaga atgcagggtc aactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggagaccatg tctttgcga cacagcagca 240
 ggaatcaatg ttgctgagca gtcaaaggag tgcaacatca acatatccac tactaattac 300
 ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactgtc tcctcttggg 360
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<210> 188
 <211> 449
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 <213> Human metapneumo virus

<400> 188
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 ggaatcaatg ttgctgagca gtcaaaggag tgcaacataa acatatctac tactaattac 300
 ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactatc tcctcttggg 360
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<210> 189
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 189
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<210> 190
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<210> 191
<211> 449
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<213> Human metapneumo virus

<400> 191
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<210> 192
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 192
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<210> 193
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 193
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atcaagcaac tgaacaaagg ctgtctta 449

<210> 194
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 194
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ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactatc tcctcttggg 360
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<210> 195

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 195

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 tacccaaatg aaaaagactg cggaaacaaga ggagaccatg tctttgcga cacagcagca 240
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 ccatgcaaag ttagcacagg aagacatcct atcagtatgg ttgcactgtc tcctcttggg 360
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<210> 196

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 196

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<210> 197

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 197

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<210> 198

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 198

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449

<210> 199
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 199
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<210> 200
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 200
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gctctagttg cttgtacaa aggagtaagc tggccattt gcagcaatag agtagggatc 420
atcaaggcgc tgaacaaagg ttgctccta 449

<210> 201
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 201
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atcaaggcgc tgaacaaagg ttgctctta 449

<210> 202
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 202
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gctctagttg cttgtacaa aggagtaagc tggccattt gcagcaacag agtagggatc 420
atcaaggcgc tgaacaaagg ttgctctta 449

<210> 203
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 203
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atcaaggcgc tgaacaaagg ttgctctta 449

<210> 204
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 204
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atcaaggcgc tgaacaaagg ttgctctta 449

<210> 205
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 205
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<210> 206
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 206
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<210> 207
<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 207

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<210> 208

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 208

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<210> 209

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 209

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<210> 210

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 210

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<210> 211

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 211
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<210> 212
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 212
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<210> 213
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 213
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<210> 214
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 214
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<210> 215
<211> 449
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<213> Human metapneumo virus

<400> 215
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 atcaaacaat tacccaaagg ctgctcata 449

<210> 216
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 216
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 gcttgggtgg cttgtataa agggtaagc tgctcgattg gcagcaatcg gggttggaaatc 420
 atcaaacaat tacctaaagg ctgctcata 449

<210> 217
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 217
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 ccatgcaaag tcagcacagg aagacaccct ataagcatgg ttgcactatc acctctcggt 360
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<210> 218
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 218
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 gcttcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
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 ccatgcaaag tcagcacagg aagacaccct ataagcatgg ttgcactatc acctctcggt 360
 gcttgggtgg cttgtataa agggtaagc tgctcgattg gcagcaatcg gggttggaaatc 420
 atcaaacaat tacctaaagg ctgctcata 449

<210> 219
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 219
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 ccatgcaaag tcagcacagg aagacactct ataagcatgg ttgcactatc acctctcggt 360
 gcttgggtgg cttgtataa agggtaagc tgctcgattg gcagcaatcg gtttggaaatc 420
 atcaaacaat tacctaaagg ctgctcata 449

<210> 220
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 220
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gcttgcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
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ccatgcaaag tcagcacagg aagacaccct ataagcatgg ttgcactatc acctctcggt 360
gcttgggtgg cttgtataa agggtaagc tgctcgattg gcagcaatcg gtttggaaatc 420
atcaaacaat tacctaaagg ctgctcata 449

<210> 221
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 221
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gatacacctt gttggataat caaggcagct ccctcttgct cagaaaaaaaaa cgaaaaattat 120
gcttgcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
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ccatgcaaag tcagcacagg aagacaccct ataagcatgg ttgcactatc acctctcggt 360
gcttgggtgg cttgtataa agggtaagc tgctcgattg gcagcaatcg gtttggaaatc 420
atcaaacaat tacctaaagg ctgctcata 449

<210> 222
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 222
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gatacacctt gttggataat caaggcagct ccctcttgct cagaaaaaaaaa cgaaaaattat 120
gcttgcctcc taagagagga tcaagggtgg tactgtaaaa atgcaggatc cactgtttac 180
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ccatgcaaag tcagcacagg aagacaccct ataagcatgg ttgcactatc acctctcggt 360
gcttgggtgg cttgtataa agggtaagc tgctcgattg gcagcaatcg gtttggaaatc 420
atcaaacaat tacctaaagg ctgctcata 449

<210> 223
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 223
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gatacacctt gttggataat caaggcagct ccctcttgct cagaaaaaaaaa cgaaaaattat 120
gcttgcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
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gggatcaatg ttgctgagca atcaagagaa tgcaacatca acatatctac taccaactac 300

ccatgcaaag tcagcacagg aagacaccct ataagcatgg ttgcactatc acctctcggt 360
 gctttggtgg cttgtataa agggtaagc tgctcgattg gcagcaatcg gtttggaaatc 420
 atcaaacaat tacccaaagg ctgctcata 449

<210> 224
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 224
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 gcttgcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
 tacccaaatg aaaaagactg cggaaacaaga ggtgatcatg tttttgtga cacagcagca 240
 gggatcaatg ttgctgagca atcaagagaa tgcaacatca acatatctac taccactac 300
 ccatgcaaag tcagcacagg aagacaccct ataagcatgg ttgcactatc acctctcggt 360
 gctttggtgg cttgtataa agggtaagc tgctcgattg gcagcaatcg gtttggaaatc 420
 atcaaacaat tacccaaagg ctgctcata 449

<210> 225
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 225
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 gatacacctt gttggataat caaggcagct ccctcttgct cagaaaaaaa cggttattat 120
 gcttgcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
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 gctttggtgg cttgtataa agggtaagc tgctcgattg gcagcaatcg gtttggaaatc 420
 atcaaacaat tacccaaagg ctgctcata 449

<210> 226
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 226
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 gcttgcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
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 ccatgcaaag tcagcacagg aagacaccct ataagcatgg ttgcactatc acctctcggt 360
 gctttggtgg cttgtataa agggtaagc tgctcgattg gcagcaatcg gtttggaaatc 420
 atcaaacaat tacccaaagg ctgctcata 449

<210> 227
 <211> 449
 <212> DNA
 <213> Human metapneumo virus

<400> 227
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 gcttgcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
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 ccatgcaaag tcagcacagg aagacaccct ataagcatgg ttgcactatc acctctcggt 360
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atcaaacaat tacctaaagg ctgctcata

449

<210> 228

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 228

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 gcttcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggtgatcatg tttttgtga cacagcagca 240
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 ccatgcaaag tcagcacagg aagacacccct ataagcatgg ttgcactatc acctctcggt 360
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 atcaaacaat tacctaaagg ctgctcata 449

<210> 229

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 229

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 gcttcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
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 ccatgcaaag tcagcacagg aagacacccct ataagcatgg ttgcactatc acctctcggt 360
 gcttgggtgg cttgtataa agggtaagc tgctcgattg gcagcaatcg gtttggaaatc 420
 atcaaacaat tacccaaagg ctgctcata 449

<210> 230

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 230

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<210> 231

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 231

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 atcaaacaac tacctaaagg ctgctcata 449

<210> 232
<211> 449
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<213> Human metapneumo virus

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atcaaacaac tacctaaagg ctgctcata 449

<210> 233
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 233
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atcaaacaac tacctaaagg ctgctcata 449

<210> 234
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 234
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atcaaacaac tacctaaagg ctgctcata 449

<210> 235
<211> 449
<212> DNA
<213> Human metapneumo virus

<400> 235
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atcaaacaac tacctaaagg ctgctcata 449

<210> 236
<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 236

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 gcttcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
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 atcaaacaac tacctaaagg ctgctcata 449

<210> 237

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 237

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 gcttcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
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 atcaaacaac tacctaaagg ctgctcata 449

<210> 238

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 238

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 gcttcctcc taagagagga ccaagggtgg tattgtaaaa atgcgggatc cactgtttac 180
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<210> 239

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 239

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<210> 240

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 240

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<210> 241

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 241

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 atcaaacaac tacctaaagg ctgctcata 449

<210> 242

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 242

ataggggtct acggaagctc cgtgattac atggtccagc tgccgatctt tggtgtcata 60
 gatacacctt gttgataat caaggcagct ccctcttgg tggaaaattat 120
 gcttcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
 tacccaaatg aaaaagactg cggaaacaaga ggtgatcatg tttttgtga cacagctgca 240
 gggatcaatg ttgctgagca atcaagagaa tgcaacatca acatatctac aaccaactac 300
 ccatgcaaag tcagcacagg aagacaccct atcagcatgg ttgcactatc acctctcggt 360
 gcttggtag cttgtacaa aggggttagc tggtaatttgc gcaatcg gtttggata 420
 atcaaacaac tacctaaagg ctgctcata 449

<210> 243

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 243

ataggggtct acggaagctc cgtgattac atggtccagc tgccgatctt tggtgtcata 60
 gatacacctt gttgataat caaggcagct ccctcttgg tggaaaattat 120
 gcttcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
 tacccaaatg aaaaagactg cggaaacaaga ggtgatcatg tttttgtga cacagctgca 240
 gggatcaatg ttgctgagca atcaagagaa tgcaacatca acatatctac aaccaactac 300
 ccatgcaaag tcagcacagg aagacaccct atcagcatgg ttgcactatc acctctcggt 360
 gcttggtag cttgtacaa aggggttagc tggtaatttgc gcaatcg gtttggata 420
 atcaaacaac tacctaaagg ctgctcata 449

<210> 244

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 244

ataggggtct acggaagctc tggattac atggtccagc tgccgatctt tggtgtcata 60

gatacacctt gttggataat caaggcagct ccctcttgc t cagaaaaaga tggaaattat 120
 gcttcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggtgatcatg tttttgtga cacagctgca 240
 gggatcaatg ttgctgagca atcaagagaa tgcaacatca acatatccac aaccaactac 300
 ccatgcaaag tcagcacagg aagacacccct atcagcatgg ttgcactgtc acctctcggt 360
 gctttggtag cttgctacaa aggggttagc t gttcgattt gcagtaatcg gtttggata 420
 atcaaacaac tacctaaagg ctgctcata 449

<210> 245

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 245

ataggggctc acggaagctc t gttgatttac atggtccagc tgccgatctt t ggtgtcata 60
 gatacacctt gttggataat caaggcagct ccctcttgc t cagaaaaaga tggaaattat 120
 gcttcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggtgatcatg tttttgtga cacagcagca 240
 gggatcaacg ttgctgagca atcaagagaa tgcaacatca acatatctac caccactat 300
 ccatgcaaag tcagcacagg aagacacccct atcagcatgg ttgcactatc acctctcggt 360
 gctttggtag cttgctacaa aggggttagc t gttcgattt gcagtaatcg gtttggata 420
 atcaaacaac tacctaaagg ctgctcata 449

<210> 246

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 246

ataggggctc acggaagctc cgtgatttac atggtccagc tgccgatctt t ggtgtcata 60
 gatacacctt gttggataat caaggcagct ccctcttgc t cagaaaaaga tggaaattat 120
 gcttcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggtgatcatg tttttgtga cacagctgca 240
 gggatcaatg ttgctgagca atcaagagaa tgcaacatca acatatctac aaccaactac 300
 ccatgcaaag tcagcacagg aagacacccct atcagcatgg ttgcactatc acctctcggt 360
 gctttggtag cttgctacaa aggggttagc t gttcaattt gcagtaatcg gtttggata 420
 atcaaacaac tacctaaagg ctgctcata 449

<210> 247

<211> 449

<212> DNA

<213> Human metapneumo virus

<400> 247

ataggggctc acggaagctc cgtgatttac atggtccagc tgccgatctt t ggtgtcata 60
 gatacacctt gttggataat caaggcagct ccctcttgc t cagaaaaaga tggaaattat 120
 gcttcctcc taagagagga tcaagggtgg tattgtaaaa atgcaggatc cactgtttac 180
 tacccaaatg aaaaagactg cgaaacaaga ggtgatcatg tttttgtga cacagcagca 240
 gggatcaatg ttgctgagca atcaagagaa tgcaacatca acatatctac aaccaactac 300
 ccatgcaaag tcagcacagg aagacacccct atcagcatgg ttgcactatc acctctcggt 360
 gctttggtag cttgctacaa aggggttagc t gttcgattt gcagtaatcg gtttggata 420
 atcaaacaac tacctaaagg ctgctcata 449

<210> 248

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 248

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile

1

5

10

15

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser

20	25	30
Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln		
35	40	45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu		
50	55	60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala		
65	70	75
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser		
85	90	95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser		
100	105	110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly		
115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Asn Lys Gly Cys Ser		
145		

<210> 249

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 249

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile		
1	5	10
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser		
20	25	30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln		
35	40	45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu		
50	55	60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala		
65	70	75
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser		
85	90	95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser		
100	105	110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly		
115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Asn Lys Gly Cys Ser		
145		

<210> 250

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 250

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile		
1	5	10
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser		
20	25	30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln		
35	40	45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu		
50	55	60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala		

65	70	75	80
Gly Ile Asn Val Ala Glu Gln Ser Lys	Glu Cys Asn Ile Asn Ile Ser		
85	90	95	
Thr Thr Asn Tyr Pro Cys Lys Val Ser	Thr Gly Arg His Pro Ile Ser		
100	105	110	
Met Val Ala Leu Ser Pro Leu Gly Ala	Leu Val Ala Cys Tyr Lys Gly		
115	120	125	
Val Ser Cys Ser Ile Gly Ser Asn Arg	Val Gly Ile Ile Lys Gln Leu		
130	135	140	
Asn Lys Gly Cys Ser			
145			

<210> 251
<211> 149
<212> PRT
<213> Human metapneumo virus

1	5	10	15
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
20	25	30	
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser			
35	40	45	
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
50	55	60	
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
65	70	75	80
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
85	90	95	
Gly Ile Asn Val Ala Glu Gln Ser Lys	Glu Cys Asn Ile Asn Ile Ser		
100	105	110	
Thr Thr Asn Tyr Pro Cys Lys Val Ser	Thr Gly Arg His Pro Ile Ser		
115	120	125	
Met Val Ala Leu Ser Pro Leu Gly Ala	Leu Val Ala Cys Tyr Lys Gly		
130	135	140	
Val Ser Cys Ser Ile Gly Ser Asn Arg	Val Gly Ile Ile Lys Gln Leu		
Asn Lys Gly Cys Ser			
145			

<210> 252
<211> 149
<212> PRT
<213> Human metapneumo virus

1	5	10	15
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
20	25	30	
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser			
35	40	45	
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
50	55	60	
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
65	70	75	80
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
85	90	95	
Gly Ile Asn Val Ala Glu Gln Ser Lys	Glu Cys Asn Ile Asn Ile Ser		
100	105	110	
Thr Thr Asn Tyr Pro Cys Lys Val Ser	Thr Gly Arg His Pro Ile Ser		
Met Val Ala Leu Ser Pro Leu Gly Ala	Leu Val Ala Cys Tyr Lys Gly		

115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Asn Lys Gly Cys Ser		
145		

<210> 253
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 253

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
1	5	10	15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser			
20	25	30	
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
35	40	45	
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
50	55	60	
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
65	70	75	80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser			
85	90	95	
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser			
100	105	110	
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly			
115	120	125	
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu			
130	135	140	
Asn Lys Gly Cys Ser			
145			

<210> 254
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 254

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
1	5	10	15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser			
20	25	30	
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
35	40	45	
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
50	55	60	
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
65	70	75	80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser			
85	90	95	
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser			
100	105	110	
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly			
115	120	125	
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu			
130	135	140	
Asn Lys Gly Cys Ser			
145			

<210> 255
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 255
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
20 25 30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
35 40 45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
130 135 140
Asn Lys Gly Cys Ser
145

<210> 256
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 256
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
20 25 30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
35 40 45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
130 135 140
Asn Lys Gly Cys Ser
145

<210> 257
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 257

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 258

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 258

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 259

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 259

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45

Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 260
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 260
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
Asn Lys Gly Cys Ser
 145

<210> 261
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 261
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
Arg Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 262
 <211> 149
 <212> PRT
 <213> Human metapneumo virus

<400> 262
 Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 263
 <211> 149
 <212> PRT
 <213> Human metapneumo virus

<400> 263
 Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140

Asn Lys Gly Cys Ser
145

<210> 264
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 264
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
20 25 30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
35 40 45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
130 135 140
Asn Lys Gly Cys Ser
145

<210> 265
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 265
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
20 25 30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
35 40 45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
130 135 140
Asn Lys Gly Cys Ser
145

<210> 266
<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 266

Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
1										10					15
Phe	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Ile	Val	Lys	Ala	Ala	Pro	Ser
										25					30
Cys	Ser	Glu	Lys	Lys	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln
										40					45
Gly	Trp	Tyr	Cys	Gln	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu
										55					60
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala
										70					80
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Lys	Glu	Cys	Asn	Ile	Asn	Ile	Ser
										85					95
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser
										100					110
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly
										115					125
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu
										130					140
Asn	Lys	Gly	Cys	Ser											
															145

<210> 267

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 267

Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
1										10					15
Phe	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Ile	Val	Lys	Ala	Ala	Pro	Ser
										20					30
Cys	Ser	Glu	Lys	Lys	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln
										35					45
Gly	Trp	Tyr	Cys	Gln	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu
										50					60
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala
										65					80
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Lys	Glu	Cys	Asn	Ile	Asn	Ile	Ser
										85					95
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser
										100					110
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly
										115					125
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu
										130					140
Asn	Lys	Gly	Cys	Ser											
															145

<210> 268

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 268

Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
1										5					15

Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 269
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 269
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 270
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 270
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 271
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 271
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
Asn Lys Gly Cys Ser
 145

<210> 272
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 272
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 273
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 273
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
Asn Lys Gly Cys Ser
 145

<210> 274
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 274
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
Asn Lys Gly Cys Ser
 145

<210> 275

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 275

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 276

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 276

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Gly Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 277

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 277

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 278

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 278

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 279

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 279

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln

35	40	45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu		
50	55	60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Val Ala		
65	70	75
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser		
85	90	95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser		
100	105	110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly		
115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Asn Lys Gly Cys Ser		
145		

<210> 280
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 280		
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile		
1	5	10
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser		
20	25	30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln		
35	40	45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu		
50	55	60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala		
65	70	75
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser		
85	90	95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser		
100	105	110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly		
115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Asn Lys Gly Cys Ser		
145		

<210> 281
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 281		
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile		
1	5	10
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser		
20	25	30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln		
35	40	45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu		
50	55	60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala		
65	70	75
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser		

85	90	95
Thr Thr Asn Tyr Pro Cys Lys Val Ser	Thr Gly Arg His Pro Ile Ser	
100	105	110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly		
115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Asn Lys Gly Cys Ser		
145		

<210> 282
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 282	282		
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
1	5	10	15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser			
20	25	30	
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
35	40	45	
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
50	55	60	
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
65	70	75	80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser			
85	90	95	
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser			
100	105	110	
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly			
115	120	125	
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu			
130	135	140	
Asn Lys Gly Cys Ser			
145			

<210> 283
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 283	283		
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
1	5	10	15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser			
20	25	30	
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
35	40	45	
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
50	55	60	
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
65	70	75	80
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser			
85	90	95	
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser			
100	105	110	
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly			
115	120	125	
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu			

130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 284
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 284
 Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 285
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 285
 Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 286

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 286

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 287

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 287

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Asn Lys Gly Cys Ser
 145

<210> 288

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 288

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile

1	5	10	15												
Phe	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Ile	Val	Lys	Ala	Ala	Pro	Ser
20	25	30													
Cys	Ser	Glu	Lys	Lys	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln
35	40	45													
Gly	Trp	Tyr	Cys	Gln	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu
50	55	60													
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala
65	70	75	80												
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Lys	Glu	Cys	Asn	Ile	Asn	Ile	Ser
85	90	95													
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser
100	105	110													
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly
115	120	125													
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu
130	135	140													
Asn	Lys	Gly	Cys	Ser											
145															

<210> 289
<211> 149
<212> PRT
<213> Human metapneumo virus

1	5	10	15												
Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
20	25	30													
Cys	Ser	Glu	Lys	Lys	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln
35	40	45													
Gly	Trp	Tyr	Cys	Gln	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu
50	55	60													
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala
65	70	75	80												
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Lys	Glu	Cys	Asn	Ile	Asn	Ile	Ser
85	90	95													
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser
100	105	110													
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly
115	120	125													
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu
130	135	140													
Asn	Lys	Gly	Cys	Ser											
145															

<210> 290
<211> 149
<212> PRT
<213> Human metapneumo virus

1	5	10	15												
Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
20	25	30													
Cys	Ser	Glu	Lys	Lys	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln
35	40	45													
Gly	Trp	Tyr	Cys	Gln	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu

50	55	60
Lys Asp Cys Glu Thr Arg	Gly Asp His Val Phe Cys Asp Thr Ala Ala	
65	70	75
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser		80
85	90	95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser		
100	105	110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly		
115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Asn Lys Gly Cys Ser		
145		

<210> 291

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 291		
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile		
1	5	10
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Val Lys Ala Ala Pro Ser		15
20	25	30
Cys Ser Glu Lys Lys Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln		
35	40	45
Gly Trp Tyr Cys Gln Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu		
50	55	60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala		
65	70	75
Gly Ile Asn Val Ala Glu Gln Ser Lys Glu Cys Asn Ile Asn Ile Ser		80
85	90	95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser		
100	105	110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly		
115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Asn Lys Gly Cys Ser		
145		

<210> 292

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 292		
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile		
1	5	10
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser		15
20	25	30
Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln		
35	40	45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu		
50	55	60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala		
65	70	75
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser		80
85	90	95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser		

100	105	110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly		
115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Pro Lys Gly Cys Ser		
145		

<210> 293
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 293			
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
1	5	10	15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser			
20	25	30	
Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
35	40	45	
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
50	55	60	
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
65	70	75	80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser			
85	90	95	
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser			
100	105	110	
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly			
115	120	125	
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu			
130	135	140	
Pro Lys Gly Cys Ser			
145			

<210> 294
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 294			
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
1	5	10	15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser			
20	25	30	
Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
35	40	45	
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
50	55	60	
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
65	70	75	80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser			
85	90	95	
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser			
100	105	110	
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly			
115	120	125	
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu			
130	135	140	
Pro Lys Gly Cys Ser			

145

<210> 295
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 295

Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
1								5		10					15
Phe	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Ile	Ile	Lys	Ala	Ala	Pro	Ser
								20		25					30
Cys	Ser	Glu	Lys	Asn	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln
								35		40					45
Gly	Trp	Tyr	Cys	Lys	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu
								50		55					60
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala
								65		70					80
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Arg	Glu	Cys	Asn	Ile	Asn	Ile	Ser
								85		90					95
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser
								100		105					110
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly
								115		120					125
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu
								130		135					140
Pro	Lys	Gly	Cys	Ser											
145															

<210> 296
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 296

Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
1								5		10					15
Phe	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Ile	Ile	Lys	Ala	Ala	Pro	Ser
								20		25					30
Cys	Ser	Glu	Lys	Asn	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln
								35		40					45
Gly	Trp	Tyr	Cys	Lys	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu
								50		55					60
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala
								65		70					80
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Arg	Glu	Cys	Asn	Ile	Asn	Ile	Ser
								85		90					95
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser
								100		105					110
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly
								115		120					125
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu
								130		135					140
Pro	Lys	Gly	Cys	Ser											
145															

<210> 297
<211> 149
<212> PRT

<213> Human metapneumo virus

<400> 297

Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
1															15
Phe	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Ile	Ile	Lys	Ala	Ala	Pro	Ser
															30
Cys	Ser	Glu	Lys	Asn	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln
															45
Gly	Trp	Tyr	Cys	Lys	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu
															60
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala
															80
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Arg	Glu	Cys	Asn	Ile	Asn	Ile	Ser
															95
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser
															110
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly
															125
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu
															140
Pro	Lys	Gly	Cys	Ser											
															145

<210> 298

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 298

Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
1															15
Phe	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Ile	Ile	Lys	Ala	Ala	Pro	Ser
															30
Cys	Ser	Glu	Lys	Asn	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln
															45
Gly	Trp	Tyr	Cys	Lys	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu
															60
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala
															80
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Arg	Glu	Cys	Asn	Ile	Asn	Ile	Ser
															95
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser
															110
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly
															125
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu
															140
Pro	Lys	Gly	Cys	Ser											
															145

<210> 299

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 299

Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
1															15
Phe	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Ile	Ile	Lys	Ala	Ala	Pro	Ser

20	25	30
Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln		
35	40	45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu		
50	55	60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala		
65	70	75
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser		
85	90	95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Ser Ile Ser		
100	105	110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly		
115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Pro Lys Gly Cys Ser		
145		

<210> 300

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 300

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile		
1	5	10
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser		
20	25	30
Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln		
35	40	45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu		
50	55	60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala		
65	70	75
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser		
85	90	95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser		
100	105	110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly		
115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Pro Lys Gly Cys Ser		
145		

<210> 301

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 301

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile		
1	5	10
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser		
20	25	30
Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln		
35	40	45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu		
50	55	60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala		

65	70	75	80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser			
85	90	95	
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser			
100	105	110	
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly			
115	120	125	
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu			
130	135	140	
Pro Lys Gly Cys Ser			
145			

<210> 302
<211> 149
<212> PRT
<213> Human metapneumo virus

1	5	10	15
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
20	25	30	
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser			
35	40	45	
Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
50	55	60	
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
65	70	75	80
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
85	90	95	
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser			
100	105	110	
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser			
115	120	125	
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly			
130	135	140	
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu			
Pro Lys Gly Cys Ser			
145			

<210> 303
<211> 149
<212> PRT
<213> Human metapneumo virus

1	5	10	15
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
20	25	30	
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser			
35	40	45	
Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
50	55	60	
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
65	70	75	80
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
85	90	95	
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser			
100	105	110	
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser			
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly			

115	120	125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu		
130	135	140
Pro Lys Gly Cys Ser		
145		

<210> 304
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 304			
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
1	5	10	15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser			
20	25	30	
Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
35	40	45	
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
50	55	60	
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
65	70	75	80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser			
85	90	95	
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser			
100	105	110	
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly			
115	120	125	
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu			
130	135	140	
Pro Lys Gly Cys Ser			
145			

<210> 305
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 305			
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile			
1	5	10	15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser			
20	25	30	
Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln			
35	40	45	
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu			
50	55	60	
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala			
65	70	75	80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser			
85	90	95	
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser			
100	105	110	
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly			
115	120	125	
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu			
130	135	140	
Pro Lys Gly Cys Ser			
145			

<210> 306
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 306

Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
1					5					10				15	
Phe	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Ile	Ile	Lys	Ala	Ala	Pro	Ser
				20					25				30		
Cys	Ser	Glu	Lys	Asn	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln
		35				40						45			
Gly	Trp	Tyr	Cys	Lys	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu
						50				55		60			
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala
	65				70				75				80		
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Arg	Glu	Cys	Asn	Ile	Asn	Ile	Ser
					85				90			95			
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser
				100				105				110			
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly
				115				120				125			
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu
				130				135				140			
Pro	Lys	Gly	Cys	Ser											
	145														

<210> 307
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 307

Ile	Gly	Val	Tyr	Gly	Ser	Ser	Val	Ile	Tyr	Met	Val	Gln	Leu	Pro	Ile
1					5					10				15	
Phe	Gly	Val	Ile	Asp	Thr	Pro	Cys	Trp	Ile	Ile	Lys	Ala	Ala	Pro	Ser
				20					25			30			
Cys	Ser	Glu	Lys	Asn	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln
		35				40						45			
Gly	Trp	Tyr	Cys	Lys	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu
					50			55			60				
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala
	65				70				75			80			
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Arg	Glu	Cys	Asn	Ile	Asn	Ile	Ser
					85				90			95			
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser
				100				105				110			
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly
				115				120				125			
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu
				130				135				140			
Pro	Lys	Gly	Cys	Ser											
	145														

<210> 308
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 308

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Pro Lys Gly Cys Ser
 145

<210> 309

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 309

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Pro Lys Gly Cys Ser
 145

<210> 310

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 310

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Asn Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45

Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Pro Lys Gly Cys Ser
 145

<210> 311
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 311
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
 20 25 30
Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
Pro Lys Gly Cys Ser
 145

<210> 312
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 312
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
 20 25 30
Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95

Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Pro Lys Gly Cys Ser
 145

<210> 313
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 313
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
 20 25 30
Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
Pro Lys Gly Cys Ser
 145

<210> 314
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 314
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
 1 5 10 15
Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
 20 25 30
Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140

Pro Lys Gly Cys Ser
145

<210> 315
<211> 149
<212> PRT
<213> Human metapneumo virus

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35 40 45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
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Pro Lys Gly Cys Ser
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<210> 316
<211> 149
<212> PRT
<213> Human metapneumo virus

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35 40 45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
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Pro Lys Gly Cys Ser
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<210> 317
<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 317

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										20					25		30		
Cys	Ser	Glu	Lys	Asp	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln				
										35					40		45		
Gly	Trp	Tyr	Cys	Lys	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu				
										50					55		60		
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala				
										65					70		75		80
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Arg	Glu	Cys	Asn	Ile	Asn	Ile	Ser				
										85					90		95		
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser				
										100					105		110		
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly				
										115					120		125		
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu				
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Pro	Lys	Gly	Cys	Ser															
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<210> 318

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 318

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										20					25		30		
Cys	Ser	Glu	Lys	Asp	Gly	Asn	Tyr	Ala	Cys	Leu	Leu	Arg	Glu	Asp	Gln				
										35					40		45		
Gly	Trp	Tyr	Cys	Lys	Asn	Ala	Gly	Ser	Thr	Val	Tyr	Tyr	Pro	Asn	Glu				
										50					55		60		
Lys	Asp	Cys	Glu	Thr	Arg	Gly	Asp	His	Val	Phe	Cys	Asp	Thr	Ala	Ala				
										65					70		75		80
Gly	Ile	Asn	Val	Ala	Glu	Gln	Ser	Arg	Glu	Cys	Asn	Ile	Asn	Ile	Ser				
										85					90		95		
Thr	Thr	Asn	Tyr	Pro	Cys	Lys	Val	Ser	Thr	Gly	Arg	His	Pro	Ile	Ser				
										100					105		110		
Met	Val	Ala	Leu	Ser	Pro	Leu	Gly	Ala	Leu	Val	Ala	Cys	Tyr	Lys	Gly				
										115					120		125		
Val	Ser	Cys	Ser	Ile	Gly	Ser	Asn	Arg	Val	Gly	Ile	Ile	Lys	Gln	Leu				
										130					135		140		
Pro	Lys	Gly	Cys	Ser											145				

<210> 319

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 319

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Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Pro Lys Gly Cys Ser
 145

<210> 320
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 320
Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
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 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
 20 25 30
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 35 40 45
 Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Pro Lys Gly Cys Ser
 145

<210> 321
<211> 149
<212> PRT
<213> Human metapneumo virus

<400> 321
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 20 25 30
 Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60

Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
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 Pro Lys Gly Cys Ser
 145

<210> 322

<211> 149

<212> PRT

<213> Human metapneumo virus

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 Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
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 Pro Lys Gly Cys Ser
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<212> PRT

<213> Human metapneumo virus

<400> 323
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 20 25 30
 Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110

Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
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 Pro Lys Gly Cys Ser
 145

<210> 324
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<212> PRT
<213> Human metapneumo virus

<400> 324
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 35 40 45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
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Pro Lys Gly Cys Ser
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<212> PRT
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 35 40 45
Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
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Pro Lys Gly Cys Ser
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<210> 326

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 326

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 20 25 30
 Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
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 Pro Lys Gly Cys Ser
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<210> 327

<211> 149

<212> PRT

<213> Human metapneumo virus

<400> 327

Ile Gly Val Tyr Gly Ser Ser Val Ile Tyr Met Val Gln Leu Pro Ile
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 Phe Gly Val Ile Asp Thr Pro Cys Trp Ile Ile Lys Ala Ala Pro Ser
 20 25 30
 Cys Ser Glu Lys Asp Gly Asn Tyr Ala Cys Leu Leu Arg Glu Asp Gln
 35 40 45
 Gly Trp Tyr Cys Lys Asn Ala Gly Ser Thr Val Tyr Tyr Pro Asn Glu
 50 55 60
 Lys Asp Cys Glu Thr Arg Gly Asp His Val Phe Cys Asp Thr Ala Ala
 65 70 75 80
 Gly Ile Asn Val Ala Glu Gln Ser Arg Glu Cys Asn Ile Asn Ile Ser
 85 90 95
 Thr Thr Asn Tyr Pro Cys Lys Val Ser Thr Gly Arg His Pro Ile Ser
 100 105 110
 Met Val Ala Leu Ser Pro Leu Gly Ala Leu Val Ala Cys Tyr Lys Gly
 115 120 125
 Val Ser Cys Ser Ile Gly Ser Asn Arg Val Gly Ile Ile Lys Gln Leu
 130 135 140
 Pro Lys Gly Cys Ser
 145

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(51) International Patent Classification⁷: C12N 7/00,
A61K 39/12, 39/15

(74) Agents: CORUZZI, Laura, A. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).

(21) International Application Number:

PCT/US2003/005276

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(22) International Filing Date: 21 February 2003 (21.02.2003)

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(30) Priority Data:
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(71) Applicants (*for all designated States except US*): MED-IMMUNE VACCINES, INC. [US/US]; 35 W. Watkins Mill Road, Gaithersburg, MD 20878 (US). VIRONOVATIVE BV [NL/NL]; P.O. Box 1738, NL-3000 DR Rotterdam (NL).

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/072720 A3

(54) Title: RECOMBINANT PARAINFLUENZA VIRUS EXPRESSION SYSTEMS AND VACCINES COMPRISING HETEROLOGOUS ANTIGENS DERIVED FROM METAPNEUMOVIRUS

(57) Abstract: The present invention relates to recombinant bovine parainfluenza virus (bPIV) cDNA or RNA which may be used to express heterologous gene products in appropriate host cell systems and/or to rescue negative strand RNA recombinant viruses that express, package, and/or present the heterologous gene product. In particular, the heterologous gene products include gene product of another species of PIV or from another negative strand RNA virus, including but not limited to, influenza virus, respiratory syncytial virus, human metapneumovirus and avian pneumovirus. The chimeric viruses and expression products may advantageously be used in vaccine formulations including vaccines against a broad range of pathogens and antigens.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/05276

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 7/00; A61K 39/12, 39/15
U.S CL : 435/ 235.1, 236, 320.1; 424199.1, 202.1, 204.1, 211.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/ 235.1, 236, 320.1; 424199.1, 202.1, 204.1, 211.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98/53078 (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 26 November 1998 (26.11.98), see pages 6- 10 and examples XII and XIII.	1- 3, 22, 27- 44
Y	NISSEN, M.D. et al., Evidence of human metapneumovirus in Australian children. The Medical Journal of Australia 18 February 2002, Vol. 176, No. 4, page 188, see entire document.	1- 3, 22, 27- 44
A	SKIADAPOULOS, M.H. et al., A Chimeric Human-Bovine Parainfluenza Virus Type 3 Expressing Measles Virus Hemagglutinin Is Attenuated for Replication but Is Still Immunogenic in Rhesus Monkeys. Journal of Virology 2001 Vol. 75, pages 10498-10504.	
A	SCHMIDT, A. C. et al., Mucosal Immunization of Rhesus Monkeys against Respiratory Syncytial Virus Subgroups A and B and Human Parainfluenza Virus Type 3 by Using a Live cDNA-Derived Vaccine Based on a Host Range-Attenuated Bovine Parainfluenza Virus Type 3 Vector Backbone. Journal of Virology 2002 Vol. 76, pages 1089-1099.	
A	WO 03/043587 (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 30 May 2003 (30.05.2003).	1- 48

Further documents are listed in the continuation of Box C.

See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

12 December 2003 (12.12.2003)

Date of mailing of the international search report

01 JUL 2004

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Commissioner for Patents
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Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer

Myron G. Hill

Telephone No. 703-308-0196

INTERNATIONAL SEARCH REPORT

PCT/US03/05276

Continuation of B. FIELDS SEARCHED Item 3:

WEST and MEDLINE STN

parainfluenza, bovine, chimeric, metapneumovirus, recombinant, vaccine, leukemia, lymphoma, asthma

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